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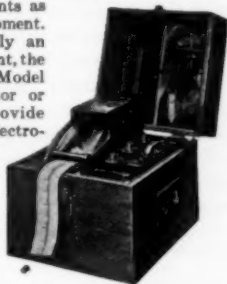
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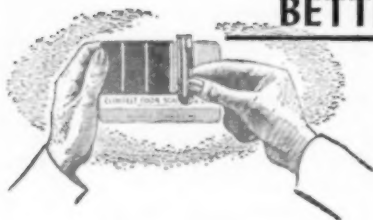
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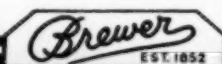
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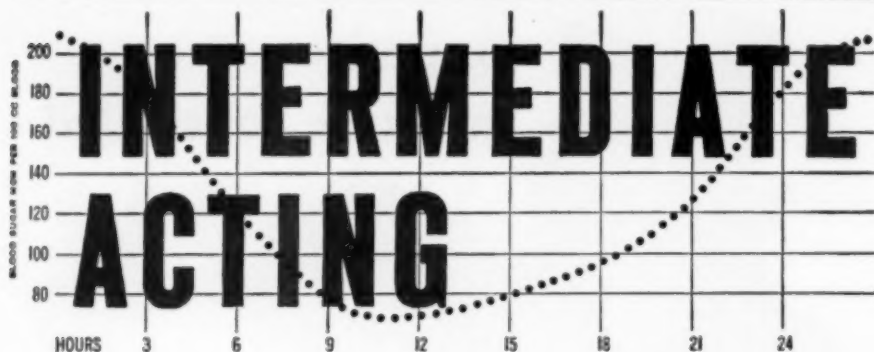
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1. Walker, W.J.: Obesity as a Problem in Preventive Medicine, U.S. Armed Forces M.J. 1:393, 1950.
2. John, H.J.: Dietary Invalidism, Ann. Int. Med. 32:595, 1950.

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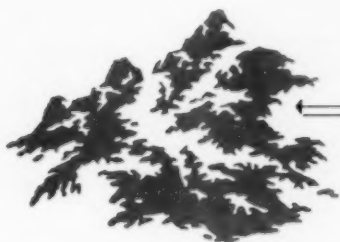
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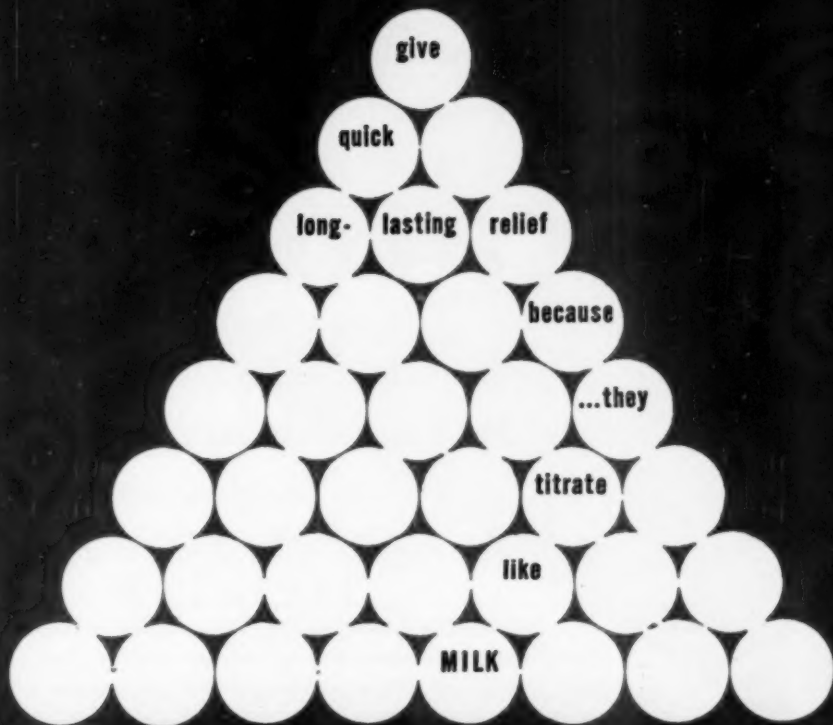
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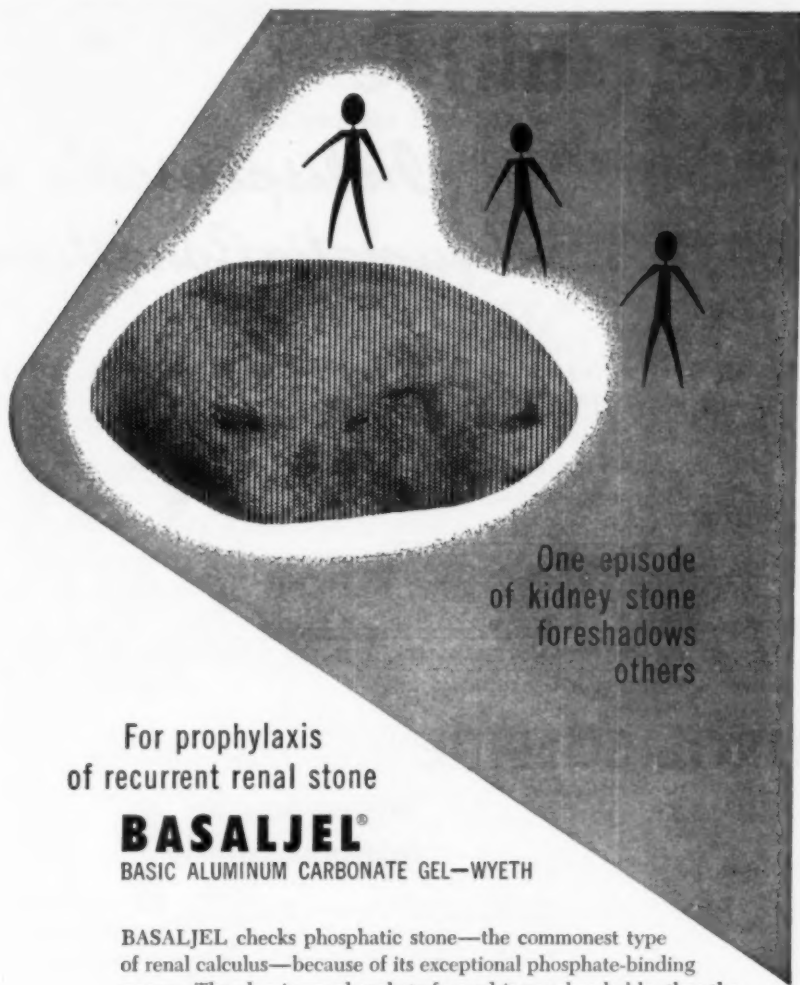
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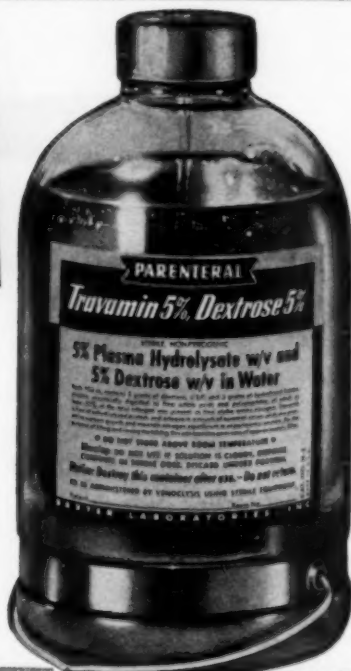
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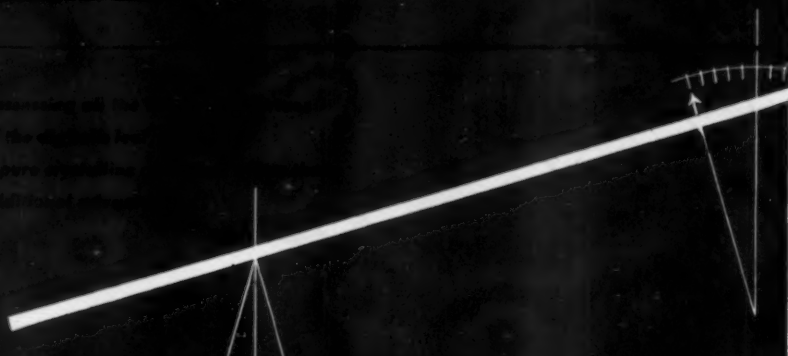
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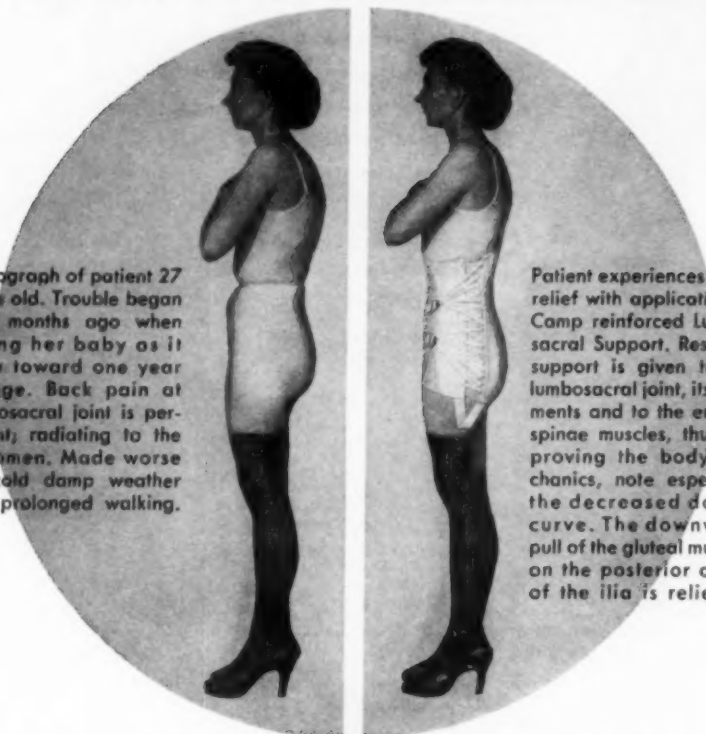
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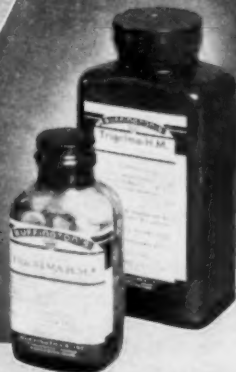
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1. Hurwitz, P.: *Am. J. Ophth.*, 31: 1409, Nov. 1948

2. Friedlaender & Friedlaender: *Ann. Allerg.*, 6: Jan.-Feb. 1948

3. Grossmann & Loring: *Am. J. of Oph.*, 32:8, Aug. 1949

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ANNALS OF INTERNAL MEDICINE

VOLUME 33

JULY, 1950

NUMBER 1

SYNTHETIC AND FERMENTATION TYPE CHLORAMPHENICOL (CHLOROMYCETIN) IN TYPHOID FEVER: PREVENTION OF RELAPSES BY ADEQUATE TREATMENT *

By JOSEPH E. SMADEL, M.D., *Washington, D. C.*, CHARLES A. BAILEY, M.D., *East Haven, Connecticut*, and RAYMOND LEWTHWAITE, M.D., *London, England*

ALTHOUGH the efficacy of chloramphenicol (Chloromycetin †) in the treatment of typhoid fever is now well established,¹⁻⁸ there are many details which require further investigation. Accordingly, additional studies on the use of chloramphenicol in this disease were continued in Malaya by our group with the following purposes in view: (a) to compare the synthetic type of drug with the fermentation type which had been employed previously, (b) to determine the adequacy of treatment when given at various stages during the course of the disease, (c) to study the usefulness of simplified therapeutic regimens, and (d) to attempt to find means of eliminating the high incidence of relapses encountered in the earlier studies.

METHODS

Selection of Patients: In general, the criteria described in the report of the earlier work in Malaya² were used in the selection of patients who were treated with chloramphenicol. A prerequisite for inclusion of a patient in this series was a positive culture for *Salmonella typhosa* from blood, urine, or feces in addition to the usual clinical evidence of typhoid fever. Practically all of these patients were treated on the wards of the Government

* Received for publication December 19, 1949.

From the Army Medical Department Research and Graduate School and the Commission on Immunization of the Army Epidemiological Board, Washington, D. C., and the Institute for Medical Research, Kuala Lumpur, Federation of Malaya.

† Chloromycetin is a trade name of Parke, Davis and Company.

hospitals in Kuala Lumpur, Federation of Malaya. Each was still in the initial attack of the disease when therapy was instituted.

Treatment: Chloramphenicol prepared by the microbiological fermentation process⁹ and by chemical synthesis¹⁰ was supplied by Parke, Davis and Company. The therapeutic regimen employed, irrespective of the type of chloramphenicol given, consisted of an initial oral dose of 3.0 to 4.0 grams of drug for adults followed by 3.0 grams daily until the temperature reached normal levels, after which 1.0 or 2.0 grams were given daily for a variable period of time.

Plan of Study: The 23 patients with typhoid fever included in the present study were placed in one of three experimental groups. Eight persons in experiment 1 received the synthetic form of drug. Blood cultures from each of these were positive for *S. typhosa* prior to treatment. These eight patients were divided into two equal subgroups, one of which was treated during the second week of disease and the other during the third to fifth week. In experiment 2 the group consisted of 12 patients each of whom had a positive culture of *S. typhosa* from blood, feces, or urine before treatment was begun. These were consecutive admissions representing unselected cases which were treated as soon after hospitalization as the diagnosis was established, varying from 8 to 67 days after onset of the disease. The members of this group were treated with either synthetic or fermentation type of drug. Experiment 3 consisted of three patients who were treated with fermentation chloramphenicol by practicing physicians in the Federation, with general advice and laboratory studies by our group. These, like the patients in the second experiment, represented the usual type of disease encountered in hospital practice in Malaya.

Clinical and Laboratory Procedures: The clinical and laboratory methods employed in the present studies were the same as those described in an earlier report.² Here, as previously, an oral temperature of 99.0° F. or higher was regarded as fever.

RESULTS

Efficacy of Synthetic Chloramphenicol in Typhoid Fever: Table 1 summarizes certain results obtained in experiment 1 in which carefully selected patients with typhoid fever were treated early and late in the course of the disease with the synthetic form of chloramphenicol. Detailed data on these patients as well as on all others in the present studies are given in appendix 1. In general, the response of patients who received the synthetic drug was as satisfactory as would have been expected had the original fermentation type of antibiotic been employed. Furthermore, in the small subgroups of this experiment, treatment was apparently as effective when given during the third to the fifth week as it was when given earlier. The duration of fever after therapy was begun was approximately the same in members of the two groups with the exception of patient 25 whose 10 day febrile disease was prolonged by intestinal perforation. Patient 28, whose course was

complicated by transient auricular fibrillation, was afebrile before and during the period of cardiac arrhythmia. The records of both these individuals are discussed in detail in a subsequent section.

The typical clinical response obtained with synthetic drug in the treatment of typhoid fever during the second week of disease is illustrated by patient 32

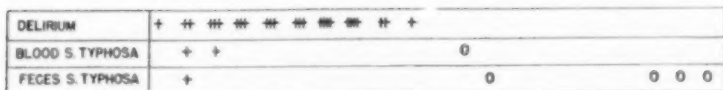
TABLE I
Results Obtained with Synthetic Chloramphenicol Given Early and Late
in Typhoid Fever

TREATMENT		DAYS OF FEVER AFTER R_x BEGUN	COMPLICATIONS
DAY OF DISEASE BEGUN	DURATION IN DAYS		
8	13	5	NONE
9	13	2	NONE
10	8	3	NONE
11	11	5	AURICULAR FIBRILLATION
16	12	7	NONE
17	12	2	NONE
18	14	10	INTESTINAL PERFORATION
31	12	5	NONE

whose record is presented graphically in figure 1 and discussed in some detail in the following paragraph.

Patient 32. This 15 year old Chinese male entered the hospital on the fifth day of an illness which had been characterized from the beginning by headache, chills, fever, and malaise, and for several days before admission by watery diarrhea. The significant physical findings were limited to those of dehydration and severe toxemia including delirium. On the sixth day of illness *S. typhosa* was recovered from the blood and feces but not from the urine; the white blood cell count was 5,000. On the afternoon of the eighth day a single oral dose of 3.0 grams of synthetic chloramphenicol was given and this was followed by 0.25 gm. every two hours for the ensuing six days. Although the temperature approached the normal range at the end of the second day of therapy, the patient did not become permanently afebrile until the fifth day of treatment. The delirium did not diminish step by step as the temperature fell by lysis. In fact, on the fourth day of treatment, when the temperature remained below 100.0° F., delirium was more intense than it had been previously when the temperature was 104.0° F. In this case, as in other treated typhoid patients, the mental state began to clear when the temperature remained near the normal range for a day or so. On the fourteenth day of illness the drug schedule was changed to 0.25 gm. every four hours and this was continued through the twentieth day. The

A comparison of the results obtained with synthetic chloramphenicol in experiment 1 with those previously reported² for a similar group of carefully selected patients who received the fermentation type of drug for a period of 8 to 14 days is given in table 2. Inspection of the table reveals that



there is no appreciable difference in the efficacy of the two forms of drug when used under relatively comparable conditions. These findings agree with the results of other studies which showed that both forms of chloramphenicol had the same degree of antibiotic activity against microbial agents in the laboratory and in patients with scrub typhus.¹¹

Patients treated after experiment I had been completed were given that form of drug which was available, but each patient was maintained throughout the period of therapy on a single type of antibiotic. In subsequent sec-

tions of this report groups of patients will be discussed without regard to the type of chloramphenicol which was used.

Comparative Efficacy of Frequent and Infrequent Daily Doses of Chloramphenicol: In the earlier studies on typhoid fever and in experiment 1 attempts were made to maintain a relatively constant and high blood level of chloramphenicol until the patient became afebrile, and a constant but somewhat lower level for a period of time thereafter. Accordingly, 0.25 gm. doses of drug were given at intervals of two to three hours throughout the day and night during the early phase of illness and at four to six hour intervals in the later stages. Such a schedule was inconvenient, especially since nursing facilities were limited. In an attempt to simplify the procedure, a number of patients were given the same total daily dose which had previously been used but they received the drug in two divided doses at 12 hour intervals during the febrile period and in a single dose once daily after the temperature became normal. The results obtained in eight of these patients (36 to 39

TABLE II
Comparative Efficacy of Synthetic and Fermentation Chloramphenicol in Patients with Typhoid Fever Who Were Treated for Eight to 14 Days

TYPE DRUG	NUMBER OF PATIENTS	MEAN DAY OF DISEASE R _e STARTED	TREATMENT		FEBRILE DAYS AFTER R _e STARTED	NUMBER OF RELAPSES
			TOTAL GMS (AV)	TOTAL DAYS (AV)		
SYNTHETIC	8	15	25.8	11.8	4.8	1
FERMENTATION	16*	12	23.6	9.8	3.4	1

* Data from records of patients Nos. 1-7, 9, 10, 13, 14, 17-20 and 22, reported by Woodward, Smadel and Ley.²

and 41 to 44 in appendix 1) showed that the simplified schedule gave as satisfactory results as had been obtained earlier. The record of patient 42, which is summarized graphically in figure 2, illustrates the response obtained when the drug was given once or twice daily.

Patient 42. This 18 year old Chinese male was hospitalized on the eighth day of an illness presenting the usual clinical picture of typhoid fever. *S. typhosa* was cultivated from the blood and feces but not from the urine prior to the initiation of treatment on the eleventh day of illness. The patient received an oral dose of 3.0 grams of synthetic chloramphenicol on the afternoon of the eleventh day and 1.5 grams on the morning of the twelfth day. Throughout the remainder of the febrile period, which lasted through the fourteenth day, morning and evening doses of 1.5 grams of chloramphenicol were administered. The patient remained afebrile from the fifteenth day onward. He received 1.5 grams of drug each morning from the fifteenth to the twenty-second day and 1.0 gm. daily from the twenty-third to the twenty-ninth day inclusive. The patient made an uneventful recovery and was discharged from the hospital on the fifty-fourth day. Between the fourteenth and fifty-fourth day frequent cultures of feces and urine were made and all gave negative results for *S. typhosa*.

PATIENT NO. 42
MALE, AGE 18
80 LBS.

TEMPERATURE
DEG F

CHLORAMPHENICOL
DOSE
GM/DAY

DAYS OF DISEASE

1.0 GM DAILY
TO 29TH DAY

BLOOD S. TYPHOSA	+	0							
FECES S. TYPHOSA		+	+	0	0	0	0	0	0

same individual during periods when he was receiving drug at 12 hour and at 24 hour intervals. As was to be expected, the levels fluctuated widely when relatively large doses of drug were administered to typhoid patients once or twice daily. The tabular data show that on the 12 hour schedule appreciable amounts of drug, namely, 11 to 24 gamma per c.c., were still present in the blood at the time the next dose was given. In contrast, at the end of 24 hours there was little or no drug present in the blood of those who received a single daily dose. As a corollary to these observations it is seen that the blood levels at six hours were somewhat higher in the patients on a twice daily schedule than in those on a single daily dose.

Relation of Relapses to Duration of Treatment: Our early experience with chloramphenicol in the treatment of patients with typhoid fever,^{1,2} like that of McDermott,³ indicated that relapses were more common in these patients than in those who ran the full course of the disease without benefit of specific therapy. As observations accumulated, it appeared that the incidence of relapses was highest in that group which had received the smallest amount of drug over the shortest period of time. With this idea in mind, the duration of therapy was gradually prolonged. Table 4 summarizes the information on 44 patients with typhoid fever who received chloramphenicol for varying periods of time. This group includes 22 of the present patients listed in appendix 1 and 22 of the 24 patients mentioned in an earlier report.² Two patients from the earlier report were omitted from consideration be-

TABLE III
Blood Levels of Chloramphenicol in Patients Receiving One or Two Doses Daily

SINGLE DOSE OF CHLORAMPHENICOL IN MILLIGRAMS PER KILOGRAM OF BODY WEIGHT AT INDICATED TIME INTERVAL	MICROGRAMS OF CHLORAMPHENICOL PER MILLILITER OF BLOOD				
	TIME INTERVALS BETWEEN DOSES				
	12 HOURS		24 HOURS		
	TIME IN HOURS AFTER ADMINISTRATION OF DRUG				
	6	12	6	12	24
30	41		18	8	0
	34	11	28	15	4
			13		0
			27		3
40	48	24	33	8	0
60	31	19			
80			24	20	

cause they were first treated during a relapse of the disease. Similarly, patient 40, appendix 1, is not included since he died during the course of the initial disease. The patients on whom information is given in table 4 have been grouped according to the duration of treatment; further subdivision according to the type of chloramphenicol or the schedule by which it was administered did not appear warranted. The total daily dose of drug given to each of the 44 patients, as calculated on the basis of body weight, did not vary appreciably at comparable periods during the first week of treatment.

In general, the patients included in groups A and B in table 4 were those who were carefully selected and treated early in the course of their disease. The composition of the two groups was relatively homogeneous and the patients differed mainly in the duration of their therapy. The majority of the persons included in group C were from the unselected series of typhoid

patients who represented consecutive hospital admissions. On the average, treatment was started on the patients in groups A and B on the thirteenth day of illness and in group C on the twentieth day. The patients in group A received drug over a period of four to eight days, those in B from 9 to 14 days and those in C from 14 to 19 days.

Table 4 shows that all relapses occurred in patients of group A who were treated for a period of eight days or less. Data not included in the table indicate that the clinical relapse began between 8 and 16 days, average 11, after therapy had been stopped, and that it occurred between 26 and 44 days, average 32, after onset of disease. The development of recrudescence disease in seven of these 13 patients in group A gives a relapse rate which is approximately four times that reported by Stuart and Pullen¹³ and by McCrae¹⁴ in typhoid patients who suffered the full course of the disease without benefit of specific therapy. Since no relapses occurred in groups B and C, both regi-

TABLE IV
Relation of Relapses of Typhoid Fever to Duration of Chloramphenicol Treatment

PATIENTS		TREATMENT WITH CHLORAMPHENICOL					RELAPSES	
		DURATION OF TREATMENT		ADMINISTRATION				
GROUP	NUMBER	GENERAL PERIOD	TOTAL DAYS (AVERAGE)	DAY OF DISEASE STARTED (AVERAGE)	STOPPED (AVERAGE)	TOTAL GRAMS GIVEN (AVERAGE)	NUMBER OF PATIENTS AFFECTED	PERCENT OF PATIENTS AFFECTED
A	13	8 DAYS OR LESS	6.9	13.5	20.4	20.0	7	53.8
B	19	9 TO 14 DAYS	11.2	13.7	24.9	25.7	0	0
C	12	LONGER THAN 14 DAYS	18.0	20.8	38.8	32.8	0	0

mens were equally effective in preventing relapses. The tabular data add weight to our earlier suggestion² that "... chloramphenicol apparently only suppresses the growth of the organism; ultimate recovery seems dependent on the development of immunity in the host."

Complications and Their Management. *Intestinal Hemorrhage:* Intestinal hemorrhage was the most common complication encountered in the present group of 23 patients. It occurred in five persons (patients 34, 35, 40, 43, and 45 in appendix 1) between the twelfth and twenty-second day of disease which in three instances (patients 35, 40, and 45) was before treatment was started. A member of this last group (patient 40) bled repeatedly before and after chloramphenicol was administered; he subsequently suffered intestinal perforation and died. Two others ceased bleeding before therapy was given and this complication did not recur. Patient 43 had not yet become afebrile as a result of treatment when hemorrhage oc-

curred while patient 34 had been free of fever for a day when bleeding developed. Hemorrhage was of sufficient severity to induce shock in three of the patients. Blood transfusions given to two of these were apparently helpful but proved of little value to patient 40 who had additional complications.

Intestinal Perforation: The records of the two patients who had intestinal perforation are of sufficient interest to discuss at some length.

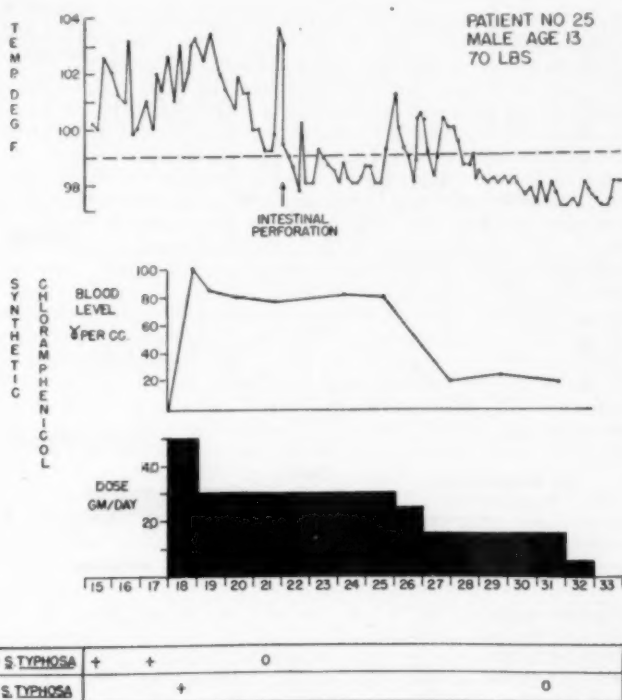


FIG. 3. Typhoid patient who suffered intestinal perforation on the twenty-first day of disease while receiving chloramphenicol and who recovered without surgical treatment.

Patient 25. This 13 year old Chinese male, whose record is presented graphically in figure 3, was hospitalized on the fifteenth day of a disease which was characterized by headache, cough, diarrhea and periods of delirium. Rose spots, pulmonary râles, splenomegaly and mental confusion were noted on physical examination. Blood and feces, obtained before treatment was begun on the eighteenth day, yielded *S. typhosa* on culture; the urine gave negative results. The patient received the synthetic form of drug with an initial dose of 4.0 grams followed by 0.25 gm. every two hours. The temperature came down by lysis on the second and third days of treatment and on the morning of the twenty-first day of illness, it approached normal. At noon

the patient experienced a chill and his fever rose to 103.6° F. No obvious cause was found for these signs, and because the temperature promptly returned to normal, undue emphasis was not placed on the episode. However, later that day the patient complained of generalized abdominal pain and refused to take the fluid diet which he had accepted previously. Physical examination at that time showed marked abdominal distention, and palpation revealed extensive muscular spasm of the abdominal wall and diffuse tenderness. Intestinal perforation was suspected. During the ensuing 24 hours, definite signs of pneumoperitoneum appeared and the amount of

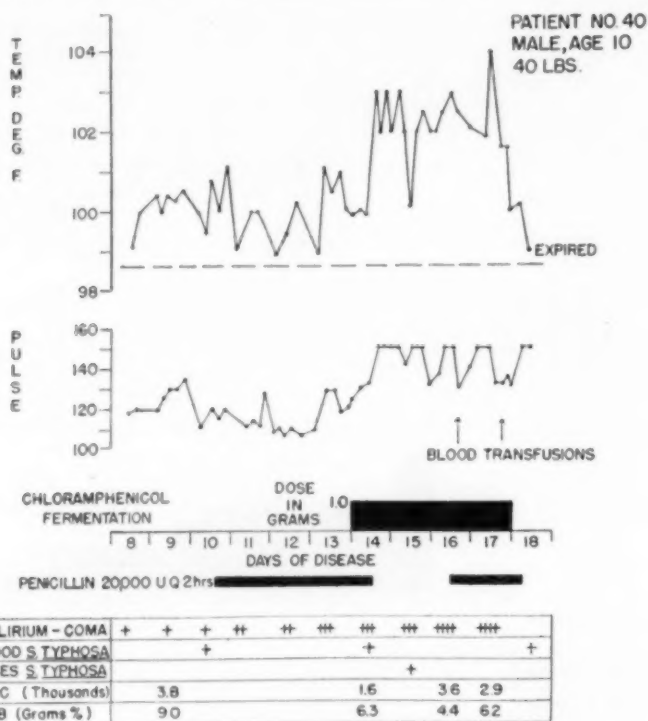


Fig. 4. Patient with typhoid fever who died while receiving chloramphenicol. In addition to intestinal bleeding and pneumonia, autopsy revealed a perforated intestine.

air apparently increased. Despite the white blood cell count of 2,100, it was our opinion, as well as that of several consultants, that the diagnosis of intestinal perforation with generalized peritonitis was warranted and that operative intervention was indicated. Permission for the operation was not obtained until the following day and by then the patient seemed to be improving. Since under similar circumstances an earlier case of typhoid with intestinal perforation had been managed successfully on chemotherapy alone,² and since the present patient was improving on a similar regimen, it was decided to avoid surgery. Throughout this episode and for the next few days the patient received 0.25 gm. of chloramphenicol orally every two hours.

In addition, at the time when surgical intervention had been decided upon, the patient was given intramuscularly a total of 650,000 units of penicillin and 3.0 grams of streptomycin, but these antibiotics were not administered subsequently. The physical signs which had led to the diagnosis of perforation and peritonitis disappeared over the next three or four days and on the tenth day of treatment the patient became permanently afebrile. He continued to receive 0.25 gm. of drug every four hours for another three days after which chloramphenicol was discontinued. Although convalescence was uneventful, the patient was kept in the hospital for observation for another month. During this time repeated cultures of feces and urine were negative for *S. typhosa*.

Patient 40. This 10 year old Chinese male was hospitalized on the eighth day of a febrile illness. He had a mild fever of 99° to 101.0° F. with a pulse rate of approximately 120. The white blood cell count was 3,800 and the hemoglobin 9.0 grams per cent. A blood culture taken on the tenth day of illness was positive for *S. typhosa*. The low grade fever continued but the patient became increasingly toxic. Penicillin was administered at the rate of 20,000 units every three hours from the tenth to fourteenth day of disease. Hematemesis and tarry stools were noted on several occasions during this period. The significant physical signs remained limited to pulmonary râles, splenomegaly and semi-coma. The patient was seen by our group on the fourteenth day of disease at which time he was semi-delirious and had temperature of 103.0° F., a pulse rate of 160, a white blood cell count of 1,650 and a hemoglobin of 6.3 grams per cent. The findings on physical examination were essentially those listed at the time of admission. He was given an oral dose of 1.0 gm. of fermentation type chloramphenicol on the fourteenth day and this was followed with 0.5 gm. doses every 12 hours. The fever and pulse continued to range around 103.0° F. and 160, respectively. Forty-eight hours after treatment was started a state of shock developed. The pulse was of poor quality, the blood pressure was 90/40, hemoglobin was 4.4 grams per cent and the white blood cell count was 3,600. Moderate abdominal distention was noted without tenderness or rigidity. During the succeeding 24 hours he received two transfusions each of 200 c.c. of whole blood. The chloramphenicol therapy was continued, and in addition, 20,000 units of penicillin were administered intramuscularly every two hours. The patient repeatedly vomited small amounts of coffee ground material and passed several small, tarry stools during this period. His condition deteriorated progressively; signs of pneumonia developed, shock continued despite the transfusions, the temperature fell, and the patient died on the eighteenth day of illness or the fourth day after treatment was instituted.

Patient 40 had received his last 1.0 gm. dose of chloramphenicol approximately 12 hours before death. Specimens of blood, bile and spinal fluid taken at autopsy contained 13, 9, and 10 mg./c.c., respectively, of chloramphenicol. Cultures of blood, bile and spleen obtained at post mortem yielded *S. typhosa*; the blood contained only a few viable organisms while the other specimens had appreciable numbers.

Postmortem examination was performed by members of the hospital staff 10 hours after death. The initial dissection was made by a diener before the arrival of a member of our group but the main pathological changes were still evident. The peritoneal surfaces were smooth and glistening. The cavity contained a few hundred c.c. of serous fluid and, in addition, in the right iliac fossa there were several small masses of fecal material which totaled about 5.0 grams in weight. Careful examination and questioning of the diener left little doubt that the fecal material was present at the time the abdominal cavity was opened. The wall of the terminal ileum, about six inches from the ileocecal valve, showed a perforation with a diameter of about 1 centimeter. The deficiency in the wall was plugged completely by a mass of inspissated feces which protruded from within the intestinal lumen.

The intestine in the region of the perforation showed remarkably little evidence of inflammatory reaction of the serosa. Up to within about 2 centimeters of the

actual defect in the wall, the serosal surface glistened normally, but within this area the surface had lost its sheen and tiny dew drop deposits were visible. The intestinal wall, for a few millimeters surrounding the margin of the perforation, was mottled with irregular small areas of hemorrhagic necrosis. A cut section through the intestine at the site of the lesion showed that the perforation occurred at an ulcerated Peyer's patch which presented the classical picture with a raised rolled mucosal edge and a crater bare of mucosa. The necrosis which had been visible through the serosa was confined to the base of the ulcer and surrounding ring of hyperplastic lymphoid tissue. Other Peyer's patches in the terminal ileum were hyperplastic but none was the site of sloughs or ulcerations. Solitary follicles were also prominent and several showed small pin-point sloughs of the overlying mucosa.

An appreciable amount of fresh blood was found by the diener when the ileum was opened. Our examination failed to reveal any point of bleeding. The stomach contained some coffee ground material; no point of bleeding was found in the stomach or jejunum.

The remainder of the postmortem examination was essentially negative except for the presence of patches of bronchopneumonia, the finding of cloudy swelling in the myocardium and in the parenchymatous tissues of the liver and kidney, and acute splenic tumor.

Histological examination of sections revealed microscopic changes in the viscera of the type to be expected during the third week of typhoid fever.¹⁵ Hemorrhagic pneumonia with essentially no polymorphonuclear cellular reaction was found in the lung. The ulcerative lesion of the ileum adjacent to the site of the perforation extended to the muscularis and the necrotic and inflammatory reaction all but obliterated the circular muscular layer. There was a dearth of polymorphonuclear cells even in the necrotic base of the ulcer which formed the lumen of the intestine at this point. The serosal layer up to within a few millimeters of the actual defect was only slightly thickened by edema and scattered loose cellular infiltrations consisting mainly of mononuclear cells with an occasional polymorphonuclear. The mesothelium of the serosa was intact but here and there tiny masses composed of fibrin, polymorphonuclear cells and fibroblasts were attached to the surface. As the defect was approached the necrotic process extended through the muscularis with only the cells of the serosa remaining viable and these were covered with a thin layer of fresh fibrin containing an occasional polymorphonuclear cell. No acute inflammatory reaction involved the visceral peritoneum covering the liver and spleen. No microscopic lesions attributable solely to toxic effects of chloramphenicol therapy were encountered. The focal areas of necrosis in the liver, the acute degenerative lesions in the lymphoid tissue throughout the body, and the mild necrobiotic changes in the kidney and heart which were observed are characteristic of typhoid fever.

The postmortem findings in patient 40 were of particular interest since they illuminated the pathological process in a treated patient with typhoid fever complicated by intestinal perforation which was unaccompanied by generalized peritonitis. The intestinal wall beneath the ulcerated Peyer's patch had amazingly few infiltrating polymorphonuclear cells even though the necrotizing typhoidal reaction, and the subsequent slough, had laid bare the muscularis over a wide area and had penetrated to the serosa in a more limited area adjacent to the actual perforation. Since the normal anatomical relationships were disturbed when we first examined the intestine, it cannot be stated that the omentum had plastered itself over the defect. However, the sharply circumscribed inflammatory reaction of the peritoneum indicated that this must have occurred. Even in the region of the local peritonitis the reaction was comparatively mild with relatively little fibrin and few polymorphonuclears; moreover, healing had begun as evidenced by the presence of fibroblasts.

Our group has now used chloramphenicol in treating three patients with typhoid fever and intestinal perforation (patients 25 and 40 in present series

and patient 3 in earlier group²⁾ and aureomycin in one such patient¹⁶ without employing surgical intervention in any instance. It is evident from this experience that the use of chloramphenicol and aureomycin has changed markedly the course of events in patients with typhoid fever who suffer perforation of the intestine. Despite the fact that three of the four patients recovered rather rapidly and that the patient who died did not develop generalized peritonitis, one cannot say that antibiotic therapy eliminates the need for proper surgical care. Surgery would certainly have been considered for patient 40 if the occurrence of the perforation had been recognized during life.

Other Complications: Complications of different types were noted in three other patients in the present series. Patient 33 had been receiving chloramphenicol for three days and her temperature had dropped by lysis when she developed physical and roentgenological signs of bronchopneumonia accompanied by a fever of 103.0° F. Chloramphenicol therapy was continued and, in addition, she was given 400,000 units of penicillin over a period of 28 hours. The patient became afebrile before the end of the course of penicillin and remained so thereafter; the physical and x-ray signs of pulmonary lesion disappeared over a period of four days.

Patient 28 had intermittent attacks of auricular fibrillation on the eighth, nineteenth, twenty-first and twenty-third days of disease. The patient was afebrile throughout this period. He received chloramphenicol from the eleventh to the twenty-first day of disease. X-ray examination of the heart during one period of fibrillation showed no enlargement; an apical systolic murmur was present during the arrhythmias but disappeared during convalescence.

Patient 36, who had no discomfort or fever during convalescence, is included in this section because laboratory examinations revealed evidence of urinary tract infection associated with *S. typhosa*.

Patient 36. A 40 year old Javanese male with typhoid fever, proved by cultivation of *S. typhosa* from the blood on the twelfth day of fever and from the urine on the twenty-second day, was referred to our group for specific therapy on the twenty-eighth day of his illness. The next day, when chloramphenicol therapy was started, the pertinent findings were low-grade fever, emaciation and urinary abnormalities. These last consisted of moderate albuminuria, pyuria (about 100 leukocytes in uncentrifuged urine per low power field) and the presence of *S. typhosa*. There was no frequency or dysuria. Another urine specimen collected 17 hours after the first dose of chloramphenicol yielded *S. typhosa* on culture but one taken at the forty-eighth hour was negative; repeated cultures of urine and feces during the next two weeks also gave negative results. By the twentieth hour of therapy his temperature was normal. He remained afebrile and asymptomatic for the remainder of his stay in the hospital.

A week after therapy was stopped, the forty-ninth day after onset, he ran amok, knifing two neighboring patients on the ward. He received a Colle's fracture and numerous simple contusions in the process of being brought under restraint. Subsequently the patient had complete amnesia for the period covered by the short interval of mental agitation and the succeeding eight hours; thereafter, he returned to his former complacent mental state and remained so while under our observation.

Twelve days after the termination of the 16 day course of antibiotic therapy, routine examination of the urine revealed the presence of typhoid organisms, and pyuria and albuminuria were found to have recurred. During the next 10 days, the daily urine cultures continued positive. A 1.0 c.c. specimen of urine produced about 200 colonies of *S. typhosa* on an E.M.B. plate. On the sixty-sixth day of disease a second course of chloramphenicol was started; this consisted of an initial oral dose of 3.0 grams followed by 1.0 gm. every six hours for seven days. Four colonies of *S. typhosa* were observed on the culture plate inoculated with 1.0 c.c. of urine collected six hours after the first dose of chloramphenicol but the specimen collected at 24 hours was sterile. Typhoid organisms did not reappear during the 23 day period of observation which followed cessation of treatment and the patient was discharged.

Bacteriological Studies on Treated Patients: The majority of the patients in the present study were hospitalized for a longer time than in the previous work in order that material for bacteriological examination could be obtained for at least a month after the patients had become afebrile. In the current work, *S. typhosa* was not recovered from the blood of patients 24 hours after therapy was begun or subsequently except in patient 40 who died and in patients 26, 45 and 47 who had clinical relapses.

Before discharge from the hospital each of the 22 surviving patients in the present series repeatedly provided specimens of feces which did not contain *S. typhosa*. Cultural studies on 15 of the patients yielded negative results throughout the period of observation. Four persons (patients 25, 29, 30 and 32) had typhoid organisms in their feces before chloramphenicol was given but not in specimens cultured during or after treatment. Two patients (29 and 38) excreted *S. typhosa* before therapy and on several occasions during or after drug was administered. As indicated in appendix 1, the last positive cultures from these two were obtained on the twenty-sixth and nineteenth days of disease, respectively. Stools from patient 45 were not cultured before specific therapy was instituted but negative results were obtained during and after treatment until the forty-fourth day of disease when a relapse began; repeated cultures taken during and after a second course of chloramphenicol were free of typhoid organisms. Patients 26 and 47 did not excrete *S. typhosa* during or after their relapses.

Four patients in the present series had *S. typhosa* in their urine before treatment was started (appendix 1). Specimens from two of these (patients 33 and 41) did not yield pathogenic organisms during the periods of treatment or convalescence. One of the four, patient 36 who had recurrent bacilluria, was discussed at length in a preceding paragraph. Patient 37, the last member of the group, and patient 28, whose urine was not cultured prior to treatment, excreted typhoid organisms on several occasions during the seventh and ninth weeks, respectively, after onset of disease. These two were asymptomatic and afebrile at the time and their urines were normal except for the positive bacteriological findings. The bacilluria subsided promptly without additional therapy; cultures of specimens taken daily for a period of two weeks after the episodes yielded negative results. In the other patients of the present series *S. typhosa* was not recovered during treatment or convalescence.

Other Laboratory Observations: Widal tests employing type "O" antigen were performed on samples of serum obtained from each of the patients early in the course of the disease and late in convalescence. The results of these tests, which are given in appendix 1, were not considered in establishing the diagnosis of the disease. Only six of the 23 patients showed a rise in antibody titer during convalescence. The titers in two patients were consistently below 1/50 and in two others below 1/100.

The hematological findings in this group of patients were consistent with those ordinarily found in indigenous tropical populations with typhoid fever. No toxic manifestations attributable to treatment with chloramphenicol were observed.

DISCUSSION AND SUMMARY

A continuation of the studies on the use of chloramphenicol (Chloromycetin) in the treatment of patients with typhoid fever indicates that the synthetic form of the drug is as efficacious as the natural antibiotic obtained by the fermentation process from *Streptomyces venezuelae*. The same total amounts of either type drug are equally effective when given in divided doses at two to six hour intervals or in larger doses once or twice daily.

There was a definite relationship between the duration of chloramphenicol treatment and the occurrence of relapses in typhoid fever. Slightly more than half of the patients who were treated for eight days or less had a recrudescence of the disease which began about 10 days after treatment was stopped. No relapses occurred in the groups of patients treated for longer periods of time. The present data suggest that a 14 day period of treatment is sufficient to prevent relapses. In spite of the dramatic therapeutic effectiveness in patients with typhoid fever, serious complications such as intestinal hemorrhage and perforation may be expected in treated patients since the stage is generally set for such developments before therapy is instituted and time is required for the healing of the typhoidal lesion of the intestine. In the present group of 23 patients, two had hemorrhage sufficiently severe to produce shock. In addition, two other patients suffered intestinal perforation; the course in one of these was further complicated by severe hemorrhage and the disease terminated fatally. Neither of the patients with perforation was given surgical treatment; chloramphenicol therapy controlled or suppressed the usual signs of generalized peritonitis.

On the basis of the present observations, it would appear that the adequate treatment of typhoid fever in the adult consists of an initial oral dose of 3.0 to 4.0 grams of chloramphenicol, followed by 1.5 gm. oral doses given every 12 hours during the febrile period and by single daily 1.5 gm. doses for seven days; thereafter the dose may be reduced to a single 1.0 gm. dose and continued until the fourteenth day of antibiotic therapy, after which the drug may be discontinued. Particular attention should be given to the recognition of intestinal perforation in treated patients since the classical signs of this development with the ensuing generalized peritonitis may be partially masked by the antibacterial effect of chloramphenicol.

PATIENT	PRE-TREATMENT CULTURES			INITIAL TREATMENT			COMPLICATIONS		LAST		RELAPSES			DAY OF DISEASE		WIDAL (T-O)	
	AGE	SEX	LAST	DAY OF DISEASE	TYPE	NO. OF DOSES PER DAY	PERCENTAGE OF FEVER AFTER	TYPE	ONSET	DAY OF DISEASE	ONSET	TREATMENT	DURATION OF FEVER	ONSET	DAY OF DISEASE	LAST POSITIVE CULTURE OBTAINED	AGGLUTINATION TITER
SYNTHETIC CHLORAMPHENICOL - 8 TO 14 DAY COURSE OF THERAPY																	
25	13	M	70	+	0	18	SYN	38	12	8	14	10				17	18
26	16	M	100	+	0	18	SYN	29	12	8	5				28	26	34
27	27	F	102	+	0	38	SYN	30	12	8	5				28	27	44
28	8	M	32	+	0	11	SYN	7	12	8	12	5			36	6	190
29	14	F	86	+	0	9	SYN	27	12	8	13	2			18	9	860
30	11	M	47	+	0	17	SYN	14	12	8	12	8			11	6	1700
31	16	F	62	+	0	16	SYN	32	12	8	12	7			19	26	50
32	15	M	100	+	0	8	SYN	30	12	8	13	5			23	14	1000
AVERAGE					13.0						11.8	4.8			13	12	680
SYNTHETIC AND FERMENTATION CHLORAMPHENICOL - 15 TO 23 DAY COURSE OF THERAPY																	
33	15	F	60	+	0	22	FER	34	12	1	19	4			28	19	22
34	15	F	70	+	0	18	FER	33	12	1	18	5			26	16	1000
35	37	M	100	+	0	15	FER	33	12	1	18	5			20	12	1000
36	40	M	95	+	0	29	SYN	30	2	1	15	1			30	12	66
37	14	F	78	0	+	17	FER	30	2	1	17	3			30	12	100
38	15	F	36	+	0	8	FER	21	2	1	19	11			30	12	445
39	6	F	40	+	0	13	FER	18	2	1	18	4			19	8	50
40	10	M	40	+	0	14	FER	5	2	1	18	4			17	10	220
41	44	F	85	0	+	67	FER	34	2	1	19	4			17	10	170
42	8	M	80	+	0	11	SYN	31	2	1	18	4			71	65	44
43	19	M	100	+	0	9	SYN	50	2	1	23	5			14	9	13
44	14	M	70	+	0	24	SYN	26	2	1	17	4			24	19	125
AVERAGE					21.4						18.2	4.5			28	20	760
FERMENTATION CHLORAMPHENICOL - MISCELLANEOUS																	
45	16	M	86	+	0	30	FER	21	12	8	5	3			50	44	44
46	19	M	142	+	0	19	FER	33	12	8	8	5			24	16	0
47	23	F	125	+	0	44	FER	28	12	8	6	5			4	35	200
AVERAGE					21.0						7.0	4.3			38.3	16.0	200

* SYN DENOTES SYNTHETIC CHLORAMPHENICOL
 FER DENOTES FERMENTATION CHLORAMPHENICOL

APPENDIX I

Synthetic and Fermentation Chloramphenicol in the Treatment of Typhoid Fever

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THE INFLUENCE OF A NEW BENZOIC ACID DERIVATIVE ON THE METABOLISM OF PARA-AMINOSALICYLIC ACID (PAS) AND PENICILLIN *

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THE term chemotherapy is defined by Dorland as being "the treatment of disease by administering chemicals which affect the causative organism unfavorably but do not injure the patient." This definition implies that unless a chemical has antibacterial activity and unless it is administered for the treatment of disease caused by organisms, it cannot qualify as a "chemotherapeutic" agent. According to this limited definition of chemotherapy, the new compound p-(di-n-propylsulfamyl)-benzoic acid, 'Benemid,' † is not itself a chemotherapeutic agent, but on the basis of data available at this time may be considered as an adjunct to chemotherapy with penicillin and para-aminosalicylic acid (PAS).

The need for high plasma concentrations of penicillin in the treatment of resistant infections such as subacute bacterial endocarditis and staphylococcal osteomyelitis may be met by the simple expedient of using sufficiently large quantities of penicillin. However, when the daily doses of penicillin are large, and the amounts required to increase plasma concentrations of penicillin by two- to four-fold are measured in millions of units per day, the economic aspects of treatment become very important. With regard to PAS, it is not so easy to resort to the simple measure of administering larger daily doses of the drug for the reason that nausea and vomiting are produced in the majority of patients when a dose larger than 6 to 8 gm. per day is administered. Thus the expressed desire for the attainment of higher plasma concentrations of PAS^{1,2} can seldom be realized without resort to the intravenous administration of the sodium salt of PAS,^{3,4} and this route of administration is impractical for the extended periods of time over which PAS is given in the treatment of tuberculosis. It would seem, therefore, that a drug capable of elevating and prolonging the plasma concentrations of penicillin and PAS would have practical value, especially if the agent was non-toxic and active when given in small oral doses.

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† Sharp and Dohme's trademark for p-(di-n-propylsulfamyl)-benzoic acid. This drug has been tentatively given the generic designation "probenecid."

Extensive toxicologic and pharmacologic work in mice and dogs has established the fact that 'Benemid' has a high therapeutic index.⁵ As much as 100 to 200 mg. per kg. of body weight have been administered to dogs for many months without deleterious effects. The drug is readily absorbed from the gastrointestinal tract, is bound to plasma proteins to the extent of nearly 75 per cent, and is slowly excreted in the urine in a conjugated form, probably a glucuronide. Following a single oral dose, the compound can be demonstrated in the plasma of dogs for as long as 36 hours. Investigations in dogs have shown that 'Benemid' is capable of inhibiting the excretion of penicillin, para-aminohippuric acid (PAH) and phenolsulphonthalein (PSP).⁵ Because of the pharmacologic activity and non-toxicity of this new compound as established in animals, investigations in human subjects were undertaken.

Inasmuch as there was no previous experience in human subjects, a dose of 'Benemid' was calculated that, on the basis of the available toxicologic data, would lie well within the limits of safety. Such a dose proved to be between 1 and 4 gm. per day. Single oral doses of 0.5 to 1 gm. were administered cautiously and when it was established that such doses were safe, larger amounts were given and it was found that as much as 4 gm. could be administered without producing gastrointestinal irritation or systemic symptoms. In dogs, it had been demonstrated that as little as 6 mg. per kg. of body weight resulted in the almost complete suppression of the renal tubular excretion of penicillin, and larger doses of drug did not produce any further decrease in the renal clearance of penicillin.⁵ Thus, it was anticipated that from 1 to 2 gm. of 'Benemid' might produce a pharmacologic effect in man and, accordingly, doses of this size were administered in order to determine their effect upon the penicillemia resulting from the intravenous, intramuscular, and oral administration of penicillin.

'BENEMID' AND INTRAVENOUSLY ADMINISTERED PENICILLIN

Four patients were given, intravenously, 300,000 units of sodium penicillin in aqueous solution and the penicillemia determined at one, one and one-half, two, two and one-half, four and eight hours respectively after the administration of the antibiotic agent. The following day, the same four patients were given a single oral 1 gm. dose of 'Benemid' one hour prior to the intravenous administration of a second dose of 300,000 units of sodium penicillin in aqueous solution. Blood samples were obtained at the same time intervals after the administration of penicillin and penicillin assays performed. The average penicillin plasma concentrations that were observed in these four patients are presented in figure 1. One hour after the intravenous administration of penicillin (two hours after 'Benemid') there was a twofold increase of the plasma concentrations and at the end of four hours, there was a 20-fold difference in the penicillemia influenced by 'Benemid' as compared to that seen after penicillin alone.

The four patients studied were adult males without any obvious cardiac, hepatic or renal dysfunction; their ages ranged between 19 and 43 years. It was apparent that the pharmacologic effect of 'Benemid' was established within two hours of the time that it was orally administered and that the effect was maintained for at least four hours. The prompt absorption of the drug from the gastrointestinal tract that had been observed in animals was therefore confirmed.

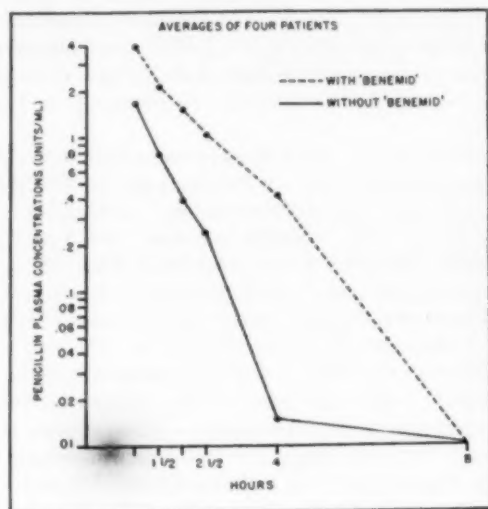


Fig. 1. Effect of single 1 gm. dose of 'Benemid' on single intravenous dose of 300,000 units sodium penicillin in aqueous solution.

'BENEMID' AND INTRAMUSCULARLY ADMINISTERED PENICILLIN

Five patients ranging in age from 16 to 36 were injected intramuscularly with 300,000 units of sodium penicillin in aqueous solution and the plasma concentrations of penicillin determined at one-half, two, four, and six hours. These same patients were then given 1 gm. oral doses of 'Benemid' every six hours for a period of 24 hours prior to the intramuscular injection of another single 300,000 unit dose of sodium penicillin in aqueous solution. Plasma concentrations of the antibiotic agent were determined at the same time intervals as previously. The results of these observations are presented for comparison in figure 2. The averages for this group of patients show that 'Benemid' produced more than a twofold increase and at the end of six hours, more than a 12-fold increase in the penicillemia observed.

The relatively insoluble procaine salt of penicillin is suspended in a number of vehicles for the purposes of prolonging the plasma concentra-

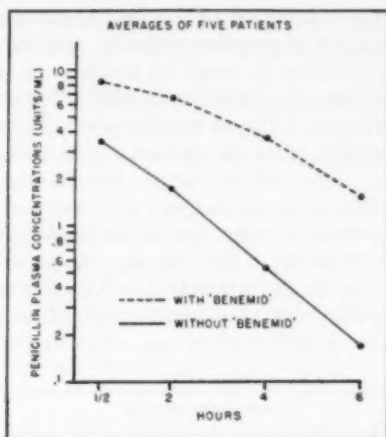


FIG. 2. Effect of 1 gm. dose of 'Benemid' repeated at six-hour intervals on single intramuscular injections of 300,000 units sodium penicillin in aqueous solution.

tions of penicillin after intramuscular injection. It was of interest to determine whether penicillin released slowly from the site of its injection might be maintained in the circulation for longer periods of time when given in conjunction with 'Benemid.' Accordingly five patients between 23 and 55 years of age were injected intramuscularly with 300,000 units of procaine penicillin in aqueous suspension. Plasma samples were obtained at one-half, one and one-half, three, and six hours thereafter and penicillin plasma con-

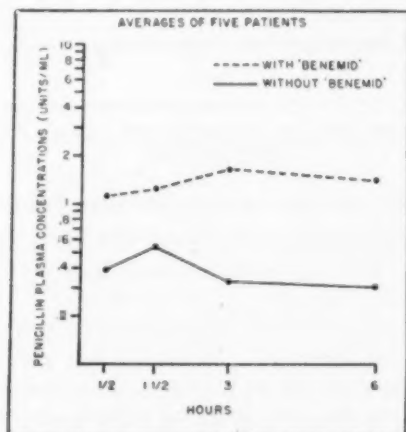


FIG. 3. Effect of 1 gm. of 'Benemid' repeated at six-hour intervals on single intramuscular injections of 300,000 units of procaine penicillin in aqueous suspension.

centrations determined. A period of 72 hours was allowed to elapse in order to dissipate the depot of procaine penicillin, and the patients were then given orally, 1 gm. of 'Benemid' every six hours for a period of 24 hours prior to a second intramuscular injection of 300,000 units of procaine penicillin in aqueous suspension. Plasma samples were obtained and the plasma concentrations of penicillin again determined. The comparative results are presented in figure 3. The tendency of the penicillemia to "plateau" both with and without 'Benemid' stands in sharp contrast to the rapidly declining slope of plasma concentrations after the intramuscular injection of sodium penicillin. This is a reflection of the retarded rate at which procaine penicillin is released from the site of its injection. It is clear that with 'Benemid' the plasma concentrations were consistently doubled as compared to those observed when procaine penicillin alone was administered.

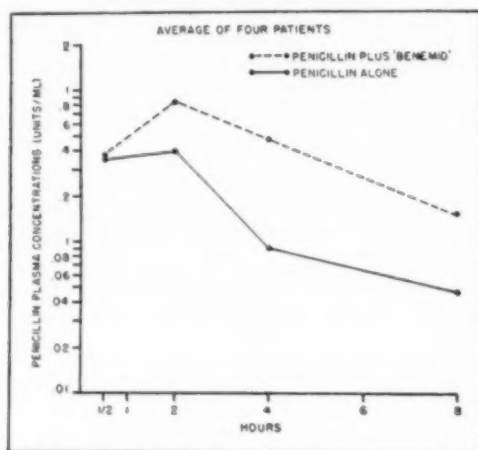


FIG. 4. Effect of single oral 2 gm. dose of 'Benemid' on single oral dose of 500,000 units penicillin.

'BENEMID' AND ORALLY ADMINISTERED PENICILLIN

Four fasting hospital patients were given 500,000 units of sodium penicillin in a single oral dose and the plasma concentrations of penicillin determined at one-half, two, four, and eight hours thereafter. On the following day, these same patients were given simultaneously 500,000 units of sodium penicillin and 2 gm. of 'Benemid.' Medication was administered with the patients in the fasting state and the plasma concentrations of penicillin were again determined at one-half, two, four, and eight hours thereafter. It is of interest to note (figure 4) that at one-half hour after the oral administration of 500,000 units of oral penicillin on two occasions, the plasma concentra-

tions were practically identical, while at two, four, and eight hours the concentrations observed after the administration of 'Benemid' were from two to seven times greater than those observed when penicillin alone was administered. The lack of difference between the plasma concentrations of penicillin observed at one-half hour is taken as evidence that a period longer than one-half hour is required for the pharmacologic effect of 'Benemid' to be established.

Six healthy adult volunteer subjects between 21 and 30 years of age were given (a) single oral doses of 500,000 units of sodium penicillin, (b) the following day, 500,000 units of sodium penicillin and 1 gm. of 'Benemid' simultaneously and (c) two days later, another single oral dose of 500,000 units of sodium penicillin. After each penicillin dose, plasma concentrations

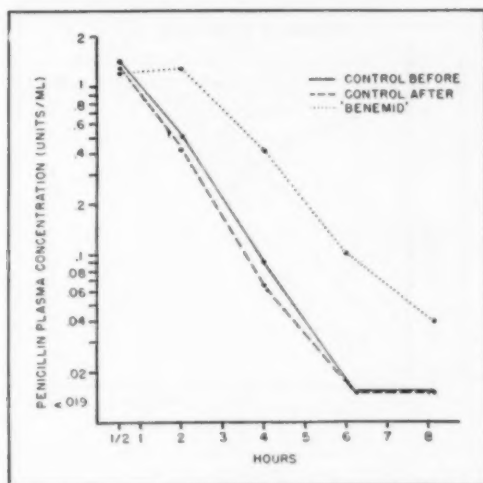


FIG. 5. Effect of single 1.0 gm. dose of 'Benemid' on single oral doses of 500,000 units of penicillin.

were determined at one-half, two, four, six and eight hours. The results obtained on these three schedules of therapy are presented in figure 5. The almost exact correspondence of the values for penicillin in the plasma observed on the two control days, one before and one after the administration of 'Benemid,' clearly demonstrates the reproducibility of results when the same human subjects are studied under carefully controlled conditions. On the day that 'Benemid' was given simultaneously with the 500,000 units of sodium penicillin, there was no enhancement effect observed at one-half hour (see also figure 4), but at two, four, six and eight hours, there were two- to fivefold increases over those that were observed when penicillin alone was administered. The reversibility of the 'Benemid' effect is attested to by the

fact that the plasma concentrations of penicillin observed after the administration of 500,000 units of sodium penicillin alone on the second day after the administration of 'Benemid' corresponded exactly with those found when the same dose of penicillin was given prior to the administration of 'Benemid.'

When penicillin was administered intravenously, one hour after the oral administration of a single dose of 'Benemid,' an enhancement effect was observed for at least five hours after the 'Benemid' had been administered, and from the evidence presented in figures 4 and 5, it is implied that an enhancement effect resulting from the administration of 1 and 2 gm. of 'Benemid' is maintained for as long as eight hours. These observations, plus the fact that it has been demonstrated that 1 gm. doses of 'Benemid' administered at six hourly intervals (figures 2 and 3) had not produced

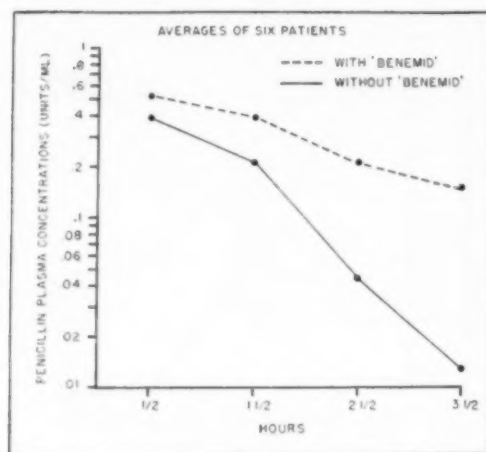


FIG. 6. Effect of 0.5 gm. doses of 'Benemid' repeated at six-hour intervals on 200,000 units oral penicillin.

enhancement effects of any greater magnitude than those observed after the single doses of the drug, makes it worthwhile to determine what the effect might be of repeated 0.5 gm. doses of 'Benemid.' Accordingly, six patients were given orally 200,000 units of sodium penicillin and plasma concentrations of the antibiotic agent determined at one-half, one and one-half, two and one-half and three and one-half hours thereafter. These same patients were then given 0.5 gm. of 'Benemid' every six hours for a period of 24 hours and the dose of penicillin was repeated. Again plasma samplings were done at the intervals stated and the degree of penicillemia determined. The results are presented for comparison in figure 6. At one-half hour there is almost a twofold difference and with the passage of time, the effect of 'Benemid' on the penicillemia became more apparent. When penicillin

alone was administered, there was barely a detectable amount of drug in the plasma at the end of three and one-half hours, whereas at the end of a similar length of time there was still 0.2 unit of penicillin per ml. of plasma when 'Benemid' was administered.

'BENEMID' AND PARA-AMINOSALICYLIC ACID (PAS)

PAS is widely used in the treatment of tuberculosis and although daily doses as large as 12 to 24 gm. a day have been administered, the majority of patients are unable to tolerate more than 6 to 8 gm. per day without the development of nausea and vomiting. This is especially true when PAS is administered in the form of the acid rather than as the sodium salt. The

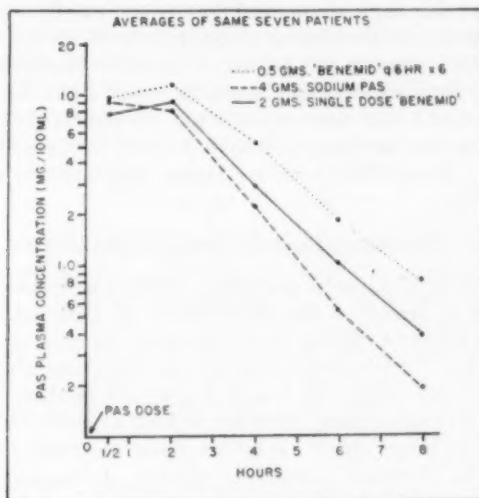


FIG. 7. PAS plasma concentrations after 4 gm. sodium PAS modified by single and repeated doses of 'Benemid.'

obvious advantage of an agent capable of prolonging PAS plasma concentrations raised the question whether or not 'Benemid' had an effect on the plasma concentrations of PAS.

Seven patients suffering from pulmonary tuberculosis who had been receiving PAS for some time were selected for this investigation. Apart from their pulmonary disease, these patients were in good condition and did not present any obvious cardiac, hepatic or renal dysfunction. All of the patients were studied under three sets of circumstances, (a) after the oral administration of a single 4 gm. dose of sodium PAS, (b) after the simultaneous administration of a single 2 gm. dose of 'Benemid' and a single 4 gm. dose of sodium PAS, and (c) after a single 4 gm. oral dose of sodium

PAS administered subsequent to 24 hours of pre-medication with 0.5 gm. of 'Benemid' every six hours. In all three phases of study, blood samples were drawn at one-half, two, four, six and eight hours after the administration of PAS, and the samples submitted for PAS determinations by the method of Way.^{5a} The summarized data are presented in figure 7. In three patients 2 gm. of 'Benemid' administered in divided doses over a 24-hour period showed greater enhancement effects on the plasma concentrations of PAS, than did a single 2 gm. dose of 'Benemid.' In one patient, the effect of these two dosage schedules was approximately equal, and in three patients, the divided dose of 'Benemid' clearly produced a greater effect than did the single dose. The averages of the seven patients under these three sets of circumstances indicate that at one-half and two hours after the administration of the single 4 gm. oral dose of sodium PAS, there were no significant differences in the plasma concentrations of PAS. This probably indicates that PAS requires this period of time for distribution within the body fluids. At four, six and eight hours, the single 2 gm. dose of 'Benemid' produced a 1.6- to 2.1-fold increase and 2 gm. administered in divided doses over a 24 hour period produced a 2.3- to 4.1-fold increase of PAS plasma concentrations. These differences are highly significant as determined by statistical analysis.

'BENEMID' PLASMA CONCENTRATIONS

In the foregoing 37 patients, penicillin and PAS have been used as reference substances to determine the effectiveness of 'Benemid.' It has been shown that the effect of 'Benemid' in retarding the rate of elimination of both penicillin and PAS is established within two hours after the oral administration of single doses of 1 and 2 gm. and furthermore that these doses maintain an enhancement effect for as long as eight hours. We have been fortunate in being able to correlate these observations with plasma determinations of 'Benemid,' since two methods of estimating the drug in body fluids are available.⁶ Although there have been technical difficulties with the methods, chiefly in connection with interfering substances that have been encountered in the plasma of some individuals, certain data of value have been accumulated. Following single oral 1 gm. doses of 'Benemid,' the drug can be demonstrated in the plasma as early as one-half hour after administration and the concentrations range from 2.5 to 5.3 mg. per 100 c.c. The plasma concentrations of 'Benemid' rise slightly during the first two hours to 5 or 10 mg. per 100 ml. and persist for at least eight hours at a range between 3 and 6 mg. per 100 ml. Single 2 gm. oral doses of 'Benemid' give rise to plasma concentrations ranging from 9 to 14 within the first hour, peak concentrations approaching 20 mg. per 100 ml. at two hours, and over a period of eight hours concentrations that decline slowly but are maintained between 5 and 8 mg. per 100 ml. In 10 patients to whom 0.5 gm. of 'Benemid' was administered every six hours, it was determined that after the fourth dose, the plasma concentrations of the drug ranged between 2 and 6

mg. per 100 ml. over the entire interval between doses. When 1 gm. of 'Benemid' was administered at six hourly intervals and plasma estimations of the drug made after the third and fourth doses, the plasma concentrations were maintained between 7 to 14 mg. per 100 ml. When 1 gm. doses of 'Benemid' were given every 12 hours, plasma concentrations between 10 and 2 mg. per 100 ml. were maintained over the 12-hour interval.

The above plasma concentrations of 'Benemid' were correlated with the effects of the drug on the plasma concentrations of both penicillin and PAS, and it appears that concentrations as low as 2 to 6 mg. per 100 ml. produce measurable effects on the plasma concentrations of these two reference substances. Concentrations of this magnitude can be maintained by the administration of 0.5 gm. of 'Benemid' at six hourly intervals, and it appears likely that in many patients concentrations of this magnitude can be maintained by the administration of 1 gm. of 'Benemid' at 12-hour intervals. Using the enhancement of penicillin plasma concentrations and the depression of PSP excretion as indices of the effectiveness of 'Benemid', it has been demonstrated that 1 gm. of 'Benemid' every 12 hours maintains a pharmacologic effect in man, but the effect may not be optimal over this entire time in all patients.

TOXICITY OF 'BENEMID'

Most of the patients studied thus far received 'Benemid' for periods no longer than 48 and 72 hours, and in no instance was more than 4 gm. per day administered. In none of the patients so studied were evidences of local or systemic toxicity observed. Five patients suffering from subacute bacterial endocarditis have received 'Benemid' in conjunction with penicillin, one received 1.5 gm. per day for 42 days, another received 2 gm. per day for 24 days, and three patients have received 2 gm. per day for 14, 28 and 30 days respectively.* In none of these patients has there been any intolerance of the drug, or evidences of system toxicity. Particular attention has been paid to the non-protein nitrogen, the urea nitrogen and the urinary findings, and no abnormalities have been observed that could not be accounted for by the disease under treatment. The suppression of the excretion of phenol-sulfonthalein (PSP) during 'Benemid' therapy is not a reflection of impaired renal function, but reflects the pharmacologic action of the drug. Phenol-sulfonthalein is excreted by the renal tubules by the same mechanism that is responsible for penicillin excretion, and this mechanism is selectively inhibited by both 'Benemid' and caronamide.⁷ Following the discontinuance of 'Benemid' therapy, the PSP excretion returns to normal within 48 hours.

DISCUSSION

The data here presented clearly indicate that a new compound, p-(di-n-propylsulfamyl)-benzoic acid, 'Benemid,' is capable of increasing, by

*Since this writing, six patients have received 2 gm. per day for eight weeks without evidence of toxicity.

two- to fourfold, the plasma concentrations of both penicillin and para-aminosalicylic acid (PAS). 'Benemid' is rapidly absorbed from the gastrointestinal tract following its oral administration and pharmacologically effective plasma concentrations are attained within two hours. The drug is slowly excreted from the body so that following single 1 and 2 gm. oral doses of 'Benemid,' an effect upon the plasma concentration of penicillin and PAS can be observed for periods up to eight hours and plasma concentrations of the drug are maintained following single doses for as long as 12 hours. The repeated administration of 0.5 to 1 gm. of 'Benemid' at intervals of every six hours maintains plasma concentration of the drug ranging between 2 and 10 mg. per 100 ml. of plasma, and this range of concentration appears to be pharmacologically effective in retarding the rate of elimination of both penicillin and PAS. These findings in man are in good agreement with the effective plasma concentrations that have been observed in dogs, 3 to 6 mg. per 100 ml.³

It is well known that a number of organic acids that are employed therapeutically are conjugated in the human body with glycine. The resulting conjugates are therapeutically inactive and are rapidly excreted by the kidneys. Such compounds are acetylsalicylic acid, benzoic acid, para-aminobenzoic acid, and para-aminosalicylic acid. If it is assumed that the conjugates of these substances are more rapidly excreted by the renal tubules than the parent substances themselves, the inhibition of the conjugation of the substances with glycine might result in a slower elimination of the parent substances from the body. It has recently been demonstrated that 'Benemid' is capable of inhibiting the conjugation of para-aminosalicylic acid with glycine that normally takes place in both liver and kidney.⁵ This laboratory evidence that 'Benemid' is capable of producing an inhibition of enzymatic system concerned with the conjugation of certain compounds with glycine, suggests that the two- to fourfold increase in the plasma concentrations of PAS that has been observed in man is a result of inhibiting the system of enzymes concerned with the conjugation of this substance. It is further proposed that the inhibition of conjugation of certain organic acids is in turn related to the renal excretory mechanism, whereby substances such as penicillin, phenolsulphonthalein (PSP), and para-aminohippuric acid (PAH) are excreted.

Caronamide (4'-carboxyphenylmethanesulfonanilide) inhibits reversibly the renal excretion of phenolsulfonthalein (PSP),⁸ penicillin^{9, 10} and para-aminosalicylic acid.^{11, 12, 13} It was originally proposed that caronamide produced a competitive inhibition of a renal tubular excretory mechanism.¹⁴ The large daily dose of caronamide that was required to produce a maximal pharmacologic effect, 18 to 24 gm. per day,¹⁵ was inconveniently large and militated against its general acceptance. Nevertheless, caronamide represented a great advance over 'Diodrast' and para-aminohippuric acid (PAH), both of which inhibit the renal excretion of penicillin but must be admin-

istered in large amounts by continuous intravenous diffusion. It is now believed that caronamide physiologically inhibits the same enzymatic systems of conjugation that are much more effectively inhibited by 'Benemid'.¹⁶ By actual test, in human subjects, it has been established that a daily dose of 2 gm. of 'Benemid' produces an effect equivalent to that produced by 24 gm. of caronamide.¹³

Inasmuch as PAS is commonly used in conjunction with streptomycin, it is natural to inquire whether 'Benemid' has any influence on the elimination of streptomycin. Comparisons of plasma concentrations in the same patients with and without 'Benemid' show that 'Benemid' has no effect on the excretion of streptomycin.¹⁷ Similarly, no effect has been observed with respect to aureomycin, Chloromycetin, or terramycin.¹⁸ Because the conjugation of PAS with glycine has been inhibited *in vitro* by 'Benemid' and the drug has an enhancing effect on the plasma concentrations of PAS as observed in man, it seemed interesting to determine whether any influence was exerted on the metabolism (conjugation) of acetylsalicylic acid (ASA). This inquiry was purposeful since acetylsalicylic acid is conjugated with glycine to form salicyluric acid.¹⁹ Preliminary data indicate that 'Benemid' has no influence on the plasma concentrations of salicylate following the administration of acetylsalicylic acid.¹⁸ This observation requires further study in view of the positive effect on PAS plasma concentrations. It may well be that in the same way as the properties of PAS were found to be unique among other salicylates investigated for their inhibition of tubercle bacilli,²⁰ 'Benemid' may have an effect on PAS and not on the salicylates. Many questions remain to be answered with regard to the application of 'Benemid' to clinical practice and to the investigation of the mechanisms whereby many drugs are eliminated, but preliminary studies indicate that this interesting compound is worthy of much study.

CONCLUSIONS

A new compound, p-(di-n-propylsulfamyl)-benzoic acid, 'Benemid,' has been described. This compound is orally effective and is capable of producing a twofold enhancement of plasma concentrations of both penicillin and para-aminosalicylic acid (PAS). The drug is readily absorbed from the gastrointestinal tract and gives rise to effective plasma concentrations of the drug within two hours. Single 1 and 2 gm. doses of the drug are effective in producing enhancement of plasma concentrations of penicillin and PAS for periods as long as eight hours. Repeated doses of 0.5 and 1 gm. every six hours maintain effective plasma concentrations of the drug, and the slow rate at which the drug is eliminated from the body permits the administration of the drug at intervals spaced as widely as every 12 hours. It is probable that plasma concentrations ranging from 2 to 10 mg. per 100 ml. will be effective in producing the full pharmacologic effect of the drug. It

is proposed that 'Benemid' produces its effect by reversibly inhibiting a system of enzymes concerned with the conjugation of certain organic acids with glycine and that the system of enzymes concerned with conjugation is related to the renal excretory mechanism whereby penicillin, para-aminohippuric acid (PAH) and phenolsulfonphthalein (PSP) are excreted. In the study of more than 50 patients, some of whom have received 1.5 gm. of 'Benemid' daily for as long as 40 days, there have been no evidences of toxicity. The oral effectiveness of the compound, the ability to administer it at widely spaced intervals, its seeming non-toxicity, and its ability to elevate by two- to fourfold the plasma concentrations of both penicillin and para-aminosalicylic acid give promise of its being of real value as an adjunct to the therapy of resistant infections amenable to intensive penicillin therapy and in the treatment of human tuberculosis.

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INFECTION OF LABORATORY WORKERS WITH COXSACKIE VIRUSES*

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A FILTRABLE agent capable of causing fatal paralysis and myositis in suckling mice and hamsters was isolated by Dalldorf and Sickles¹ from the feces of two children who had paralytic illnesses in 1947 diagnosed as poliomyelitis. Additional isolations of this agent in 1948 and its identification as a virus have been reported by Dalldorf and his associates.²

Similar viruses isolated from patients with illnesses resembling non-paralytic poliomyelitis, from another patient with an illness resembling epidemic pleurodynia, from specimens of sewage and from flies, have been under study in this laboratory since September, 1948.^{3,4} These agents have been designated as the Coxsackie group of viruses and for sake of brevity will be referred to as "C virus."

Early in 1949, three workers in the laboratory, while conducting investigations with this virus, developed febrile illnesses. During the acute stage, a virus pathogenic for infant mice was recovered from the feces of all three individuals and from the pharyngeal secretions of two of them. During convalescence all developed in their serum a capacity to neutralize this virus which was not present prior to illness.

These cases are presented because it is believed that they represent the first instances to be reported of infection with this virus in laboratory workers.

MATERIALS AND METHODS

Feces: Specimens of feces were stored at -10° C. When they were to be tested, they were thawed at room temperature. A five gram sample was homogenized in a mortar and made into a 20 per cent suspension with distilled water. This was centrifuged at 2000 R.P.M. for 20 minutes. The supernatant fluid was removed and centrifuged at a higher speed (18,000 R.P.M. for 20 minutes) and a mixture containing penicillin and streptomycin was added so that the final concentration of penicillin was 2000 u./c.c. and of streptomycin 10 mg./c.c. This suspension of feces was inoculated into infant mice less than two days of age. Each sample was inoculated into at least two litters of infant mice, including eight or more mice per

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litter. The intracerebral route of inoculation was usually used; by this route the dose was 0.01 c.c. The intraperitoneal route was equally effective, and the dose used was 0.02 c.c. The mice were subsequently observed daily for two weeks for death or signs of paralysis.

Throat Swabs: Ordinary sterile cotton tipped applicators were used to swab the throat. These were immersed in 1 c.c. of 0.01 M Na_2HPO_4 . The cotton was separated from the applicator, put into a 1 c.c. syringe, and the fluid expressed from it by repeated aspiration of the phosphate solution into the syringe. Penicillin and streptomycin were then added and this preparation was inoculated into infant mice in the same manner as described above.

In the first patient described, actual nasopharyngeal washings with serum broth were used. These were spun at 2000 R.P.M. for 10 minutes and the mixture of penicillin and streptomycin was added to the supernate. This preparation was inoculated into infant mice as described above.

Neutralization Tests: Serum was frozen and stored at -10°C . until used. The serum was then thawed and 0.2 c.c. was added to 0.2 c.c. of varying dilutions of the Connecticut No. 5 strain of C virus, which had been isolated from the feces of a patient during the summer of 1948.^{3,4} The final dilutions of virus used were 10^{-2} , 10^{-3} , and 10^{-4} . A control titration using normal monkey serum plus the virus gave an end point of 10^{-5} . The mixtures of serum and virus were allowed to remain at room temperature for one hour before inoculation of 0.02 c.c. by the intraperitoneal route into infant mice. Acute and convalescent sera were tested simultaneously. The infant mice were observed daily for two weeks for death or signs of paralysis.

CASE REPORTS

Patient 1: The patient, a 26-year-old white male physician, was admitted to the Grace-New Haven Community Hospital January 11, 1949, with the complaints of fever, weakness, anorexia, malaise, headache and sore throat. His illness had started on the evening of January 9, with malaise and anorexia. On the following day a dragging pain in the right upper quadrant of the abdomen developed which was present only on exertion. That evening while walking he had an episode of weakness, sweating, and near collapse. Fever was first noted on the evening of January 10 (figure 1).

A review of his past history revealed a story of infectious mononucleosis in 1944, with persistent splenomegaly since that time. Over a period of years the patient had developed herpes simplex whenever he had fever. During a fever of unknown origin in 1945 which lasted three days, slight icterus was noted, but the results of additional liver function tests and of red blood cell fragility tests were normal. Subsequently, the icteric index varied from 10 to 25 without other evidence of liver malfunction.

A physical examination on January 10 revealed a well-developed and well-nourished white male of 26, febrile and weak. The temperature was 104.2°F ., pulse 120 and respirations 20. The only other abnormal findings were hyperemic conjunctivae and a non-tender spleen palpable 2 cm. below the left costal margin. No adenopathy, skin rash, or abnormal neurological findings were observed.

On January 11, the left tonsil became inflamed and enlarged with an ulceration containing a small amount of yellow discharge. On January 12, lesions of herpes simplex developed on the upper and lower lips. During exacerbations of fever which began on the fifth and seventh days of illness, the patient experienced malaise, headache, and pain in the mid-back. At no time was there nuchal rigidity or a positive Kernig's or Brudzinski's sign. The patient's temperature returned to normal on the tenth day of illness, and his convalescence was uneventful thereafter.

Administration of 200,000 units of aqueous penicillin every eight hours was started on January 14, 1949, because a smear of the enlarged left tonsil was thought to reveal Vincent's organisms. There was no obvious effect of this treatment on the clinical course.

Laboratory Data: As can be seen from figure 1 the total and differential white blood cell counts were normal. A complete blood count and a urinalysis were normal on January 11. An x-ray of the chest on January 13 was normal. Tests of the

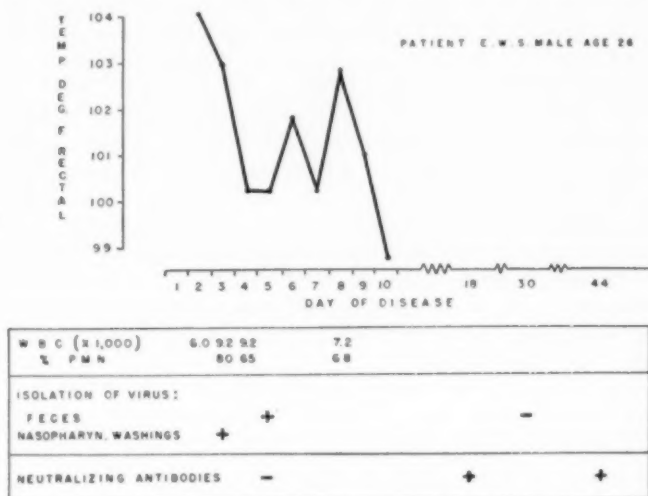


FIG. 1.

serum on January 17 for sheep cell heterophile antibody and for agglutination of enteric organisms gave negative results. Blood cultures taken at the peaks of temperature remained sterile, and nose and throat cultures failed to grow any pathogenic organisms. Because the patient at no time had meningeal signs, a lumbar puncture was not done.

The results of tests for liver function were as follows:

On January 10, serum bilirubin determinations revealed a direct reading of 0.37 mg. per cent, a total of 3.94 mg. per cent. Cephalin flocculation was negative in 24 hours and 1+ in 48 hours. On January 12, blood serum total protein was 6.37 gm. per cent with 3.26 gm. of albumin and 3.11 gm. of globulin. On January 17, serum bilirubin direct was 0.34, total 3.88. Cephalin flocculation was negative at 24 and 48 hours. Bromsulfalein retention at 45 minutes was 1.5 per cent. Thymol turbidity was 1.5 units, thymol flocculation was negative. Urine urobilinogen and urine bile tests were negative.

Virus Studies: Specimens of feces obtained from this patient were prepared and inoculated into infant mice as described above. An agent which killed or paralyzed each mouse in four separate litters of nine each, was isolated from a pool of feces collected on January 13 and January 15. This was passed by the intracerebral route through four generations of infant mice. The brain suspensions used in passage were shown to have an infectivity titer of 10^{-4} in the third passage. This agent was shown to be capable of passing through a glass-sintered disc, bacterial filter.

Nasopharyngeal washings of January 11 were similarly shown to contain the virus.

Neutralization tests were performed with the patient's serum and the strain of C virus referred to above. Serum drawn prior to illness on November 29, 1948 and an acute phase sample of January 13, 1949 failed to neutralize the virus. Specimens of serum obtained on January 26 and February 21, following recovery, both gave neutralization indices larger than 1,000.

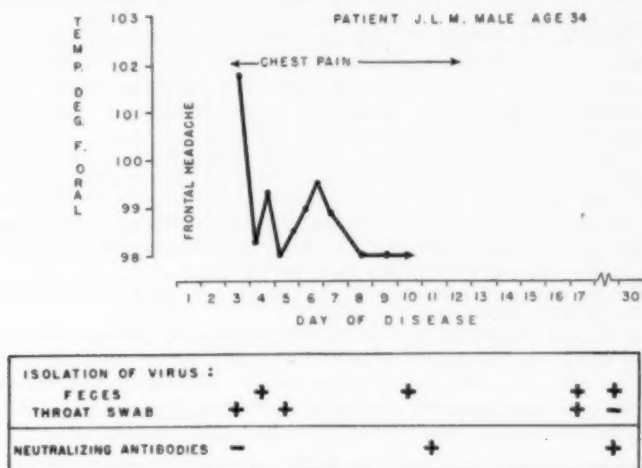


FIG. 2.

The virus was not demonstrable in specimens of feces from the patient on February 7, and April 24, 1949.

Patient 2: A 34-year-old white male investigator became ill on May 16, 1949 with a severe frontal headache (figure 2). He was asymptomatic on May 17, but on May 18, because he began to have fever, malaise and bilateral low thoracic pain, he was ordered to bed at home. The chest pain was a dull ache, present constantly, but was more severe on inspiration. The pain and headache were more distressing during the temperature elevations. After May 21, pain occurred predominantly low in the left side of the chest and occasionally low on the right side. The pain gradually subsided and after May 28 only an occasional twinge was noted. The patient resumed partial activity on May 23 and was fully active by May 27.

A review of his past history revealed no recent or similar previous illness. A physical examination on May 18 revealed a well-nourished and well-developed white male of 34, febrile and weak. His temperature (oral) was 101.8°F ., pulse 84 and respirations 20. The only other abnormal finding was minimal faucial hyperemia.

Subsequent physical examinations failed to reveal pleural friction rub, nuchal rigidity, splenomegaly, hepatomegaly, or other abnormalities.

The total white blood count on May 18 was 8000 with a normal differential count.

Virus Studies: An agent which caused paralysis and death in inoculated mice was isolated from the patient's feces on May 19, 25, June 1, 10, and 13, 1949. An identical or similar agent was obtained on three different occasions from throat swabs taken on May 18, 20, and 31, 1949. Virus was not found in a pharyngeal sample of June 10. A specimen of feces obtained prior to illness on February 21, 1949 failed to reveal the presence of the virus.

Two samples of serum obtained prior to illness on November 29, 1948 and February 21, 1949 did not neutralize the virus. Serum of May 18 showed a neutralization index of ten. Serum of May 26 showed a neutralization index larger than 1000.

Patient 3: A 24-year-old white female laboratory technician started to work in this laboratory on February 1, 1949. She had been in good health with no recent illness. On May 16, 1949 she accidentally contaminated her mouth while pipetting a 1 per cent suspension of virus (High Point, North Carolina strain).

On the afternoon of May 21, 1949 the patient noticed malaise and moderately severe pain in the right lower chest and right shoulder region. The pain was most pronounced on walking and on inspiration. During the evening of May 21, a moderately severe frontal headache developed. Fever (temperature not taken) and chilly sensations occurred during the evening of May 21.

On May 22, the malaise and chest pain persisted though to a lesser degree. Her temperature (oral) that evening was 99° F. The headache was gone. On May 23, the pain in the right lower chest shifted to the right upper quadrant of the abdomen where it seemed to be superficial and was aggravated by sneezing or coughing. The patient did not feel feverish. On May 24, malaise and abdominal cramps were noted, followed by diarrhea that evening and the following day.

A physical examination on May 25, 1949 failed to reveal any abnormalities.

A white blood count on May 25 was 7,275.

Virus Studies: Samples of feces of May 20 and May 24, 1949 both were found to contain C virus. An attempt to isolate virus from a throat swab of this patient obtained on May 19, 1949 gave negative results. Serological tests revealed no neutralization of virus by serum obtained on February 10 or May 23, 1949 but a neutralization index larger than 1000 in the serum of May 26, 1949.

Other Laboratory Personnel: In addition to the studies on the three cases described above, specimens of serum from 27 persons associated with the Section of Preventive Medicine were tested for their capacity to neutralize the virus. The serum from 18 gave negative results. Four had a neutralization index between 10 and 100. Five showed a neutralization index of 1000 or over.

DISCUSSION

Three cases have been reported of laboratory workers who developed febrile illnesses while conducting investigation with a virus pathogenic for infant mice (C virus). The virus was first isolated in this laboratory following the report by Dalldorf and Sickles¹ and has been studied continuously since September, 1948. Additional information concerning the virus and its properties, and the illnesses with which it was found to be associated, has been presented elsewhere.^{2, 3, 5, 6, 7}

In the course of these investigations, strains of C virus were isolated

from the feces of five patients who had been admitted to hospitals in Connecticut during the summer of 1948 for illnesses resembling non-paralytic poliomyelitis, and from another patient thought to have epidemic pleurodynia. Attempts to isolate the agent from nine other patients diagnosed as non-paralytic poliomyelitis or aseptic meningitis, from six patients with paralytic poliomyelitis and from 31 individuals including patients with various other illnesses were unsuccessful. Additional strains of virus pathogenic for infant mice, which were isolated from other sources including samples of feces, sewage, and flies, have also been studied in this laboratory.

All three of the investigators who became ill worked daily with infected tissues or suspensions in which C virus was present, often in high concentration. The patients, therefore, had had almost continuous exposure in the laboratory to these agents and ample opportunity to contract infection by them. In one instance (Patient 3) the onset of illness followed five days after an accidental contamination of the mouth while pipetting a suspension which contained the virus.

It has been pointed out that during the acute stage of illness, virus pathogenic for infant mice was recovered from the feces of all three of these workers and from the pharynx of two of them. Moreover, serum obtained from each of them following recovery neutralized the Connecticut No. 5 strain of virus, whereas serum obtained prior to illness or during the acute stage did not. In serum from Patient 3, obtained 10 days after an accidental aspiration of virus and only five days after the onset of symptoms, the neutralization index was larger than 1000. These findings are considered to show that the illnesses, which have been described in these workers, were probably contracted in the laboratory and were undoubtedly caused by C virus.

In all three of these patients abdominal and thoracic pain were prominent symptoms and signs of meningeal irritation were absent. None of these patients had a lumbar puncture; therefore, it was not determined whether any of them had abnormalities of the cerebrospinal fluid. In view of the findings in these three cases, it is noteworthy that several of the patients from whom virus was recovered in 1948 complained of abdominal pain, particularly one boy without nuchal rigidity who had pleocytosis of the cerebrospinal fluid and another boy with normal spinal fluid who complained of thoracic as well as abdominal pain and was considered to have epidemic pleurodynia.⁴

The findings in these cases indicate that considerable variations may be encountered in the clinical manifestations of infection by C virus and that the agent may occur in patients with illnesses resembling epidemic pleurodynia as well as in those with the syndrome of non-paralytic poliomyelitis or aseptic meningitis.

Evidence has also been obtained to suggest that infection with this virus may sometimes occur without apparent clinical manifestations. In experi-

ments carried out in this laboratory, chimpanzees excreted C virus for at least two weeks after it was fed to them and, without showing clinical signs of illness, subsequently developed in their serum the capacity to neutralize the virus. In patients following recovery from apparent infection with this virus the serological capacity to neutralize the Connecticut No. 5 strain has been found to persist in high titer for as long as eight months. It seems likely that the neutralization of this virus with serum from some of the personnel associated with the Section of Preventive Medicine indicated a response to some previous exposure to the virus. This may have occurred in the laboratory. On the other hand, the virus has also been found to be widely distributed in nature and was apparently prevalent in southern New England during 1948. Consequently, the possibility exists that, in those individuals without a history of recent illness whose serum neutralized the virus, exposure to this agent may have occurred outside of the laboratory as well as in it.

SUMMARY

Three laboratory workers developed acute febrile illnesses while studying strains of Coxsackie virus, which had been isolated from the feces of patients with illnesses resembling non-paralytic poliomyelitis.

A similar virus was recovered during the acute stage of illness from the pharynx of two and the feces of all three workers. The capacity to neutralize the virus was not present in serum prior to illness but was demonstrable in high titer in serum from each of the three workers following recovery.

ADDENDUM

In the interval since this report was written three more laboratory workers have contracted infection with strains of Coxsackie virus.

Patient 4: G. J., a 23-year-old male who had been well previously first noted slight soreness of his throat at bed-time on July 5, 1949. He had started to work in the laboratory on June 15. On July 2, he had wiped the floor about 20 minutes after his colleague F. L. had accidentally spilled a suspension of mouse tissue which was infected with a Texas type of Coxsackie virus.

On the morning of July 6, the soreness of the throat was more pronounced. Anorexia, malaise and a "tired feeling" in the legs also developed and were followed later in the day by headache, nausea, and fever. Examination revealed an elevation of temperature to 100.8° F. and moderate hyperemia of the pharynx as the only abnormal findings.

The course of illness was mild and brief. On July 7, the temperature rose to 101° F. but thereafter was normal. On July 7, the patient noted a sensation which he described as "pressure" over the eyelids, and on the following day complained of slight pain and stiffness in his neck which was not apparent on examination. His symptoms and the hyperemia of his pharynx subsided and had disappeared by July 11 except for some anorexia. He denied having had pain in the abdomen, chest, or extremities at any time during this episode.

A strain of Coxsackie virus identified as a Texas type was recovered from swabblings of the pharynx on July 6, 8, and 11 but not on July 13 nor on two later occasions. The virus was also found in specimens of feces obtained on July 9 and 11. Serum obtained from the patient prior to illness on June 15 failed to neutralize the homologous strain of virus, whereas a specimen obtained on July 25 neutralized this agent in high titer.

Patient 5: F. L., a 26-year-old laboratory worker became ill on July 17, 1949. He had started to work in the laboratory June 15. On July 2, he spilled the contents of a test tube which contained a suspension of mouse tissue infected with a Texas type of Coxsackie virus. Ethyl alcohol (95 per cent) was immediately poured over the material which later was swept up by his fellow worker, G. J.

The initial symptom on July 17 was slight soreness of the throat. On the following day this had increased and was accompanied by malaise and blurring of vision. On July 19, a temperature elevation of 100.6° F. was noted. During the next two days the initial symptoms together with aching of the extremities and fever of about 100° F. persisted. Subsequently, improvement was rapid and by July 25 recovery seemed to be complete.

Coxsackie virus (Texas type) was recovered from a throat swab collected from this patient on July 18, but not from similar specimens obtained on July 11, 21, or 25. A test for the presence of virus in feces collected on July 25 gave negative results. Serum obtained from this patient on June 15 did not neutralize the homologous strain of virus, but a specimen obtained July 25 neutralized it in high titer.

Patient 6: L. M. K., a healthy 29-year-old female investigator, while pipetting a suspension of Coxsackie virus (Ohio type) on October 15, 1949, accidentally contaminated her mouth. Two days later on October 17, she noted nasal congestion. On the following day she began to have occipital headache and to feel depressed. During October 19 she also experienced diffuse thoracic pain which lasted for one day. On October 20, she had muscular stiffness and soreness of her right shoulder with cutaneous hyperesthesia of the scapula and the ulnar aspect of that arm.

During October 21 all symptoms subsided. On October 22, however, she noted cutaneous hyperesthesia in the left leg. She had anorexia and nausea but did not vomit. Her temperature rose to 102° F. and she became aware of stiffness in the neck and back.

She was admitted to the hospital on October 24. Her temperature was 102, pulse rate 94, respirations 18, and blood pressure 110/76. Physical examination revealed no noteworthy abnormalities other than slight stiffness of the neck. The total white blood count was 7,750 with a normal distribution. A lumbar puncture yielded clear cerebrospinal fluid under normal pressure. It contained 375 leukocytes per cu. mm. of which 49 per cent were polymorphonuclear. The protein content was 31 mg. per cent. Cultures of the fluid remained sterile. An x-ray of the chest on October 24 showed no abnormality.

On October 24, the temperature rose to a peak of 103.5° F. but fell to normal by the following day. Thereafter, the course of illness was one of rapid improvement. The patient was discharged from the hospital on October 28.

Coxsackie virus (Ohio type) was recovered from a throat swab collected on October 23, although not from a similar specimen obtained on October 20. The virus was also isolated from feces collected on October 26 and 28, but not from similar specimens obtained on October 23, 30, and November 1. Tests for the presence of virus in cerebrospinal fluid obtained on October 23 and in a biopsy of skeletal muscle (left gastrocnemius) removed on October 27 gave negative results. Serum obtained from the patient prior to illness did not neutralize the virus but a specimen of October 28 did neutralize it in high titer. The development of complement-fixing antibodies against the agent was not demonstrable until three months after the onset of illness.

Among the six laboratory workers who contracted infection with Coxsackie viruses three different types of this group were represented. In each case the virus was isolated from one or more sources and the development of antibodies against the homologous and a related strain was clearly demonstrable. In each case the virus appeared to have caused the associated illness, and the evidence indicated that infection was probably contracted in the laboratory. The clinical manifestations of illness varied considerably in these patients, and in the one on whom a lumbar puncture was done, pleocytosis of the cerebrospinal fluid was demonstrated.

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MULTIPLE MYELOMA: A STUDY OF 24 PATIENTS TREATED WITH RADIOACTIVE ISOTOPES (P^{32} AND SR^{89}) *

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THE treatment of multiple myeloma has always been discouraging. As in other inoperable malignant conditions, x-ray therapy has been used wherever indicated, and the use of stilbamidine by Snapper has been successful in relieving pain due to myeloma, but no prolongation of life has been apparent.¹ Urethane has recently been used in the treatment of multiple myeloma by Loge and Rundles.² Subsidence of pain and a decrease of abnormal cells occurred in some cases. In a series of 83 patients studied by Bayrd and Heck, the average length of life in multiple myeloma was 19 months, and the duration seemed to be independent of treatment.³ In evaluating the beneficial effects of treatment of multiple myeloma, it must be kept in mind that this disease varies markedly in its rate of progression, and that temporary improvement after various forms of therapy may occur. The relatively benign cases of myelomatous proliferation characterized by solitary localization are responsive to local x-ray therapy. These tumors, besides being highly radiosensitive, may remain localized at their primary site for relatively long periods of time. Other types of myeloma spread rapidly and are not so amenable to therapy. Thus, the benefit obtained from various therapeutic agents must be considered from these points of view. The most favorable results have naturally been obtained in the cases of solitary myeloma which, as a rule, respond well to x-ray therapy, and the duration of life has probably been prolonged in these cases. In a recent review of this problem, Gootnick estimated that the duration of life in cases of solitary myeloma treated by roentgen irradiation was seven years after the onset of symptoms.⁴

Fitz-Hugh and Hodes report their experience in one case of multiple myeloma treated with radiophosphorus in which no benefit was obtained.⁵ Treatment of one case of plasma cell leukemia and three cases of plasma cell myeloma with P^{32} was reported by Warren.⁶ In the case of the plasma cell leukemia, treatment with P^{32} had no effect, and of the three cases of plasma

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cell myeloma, two were helped. Bayrd and Hall have recently reported an unusual remission in the case of acute plasma cell leukemia following P^{32} therapy.⁷

Reinhard, Moore, Bierbaum and Moore analyzed their results in eight patients with multiple myeloma treated with radioactive phosphorus, the dosage ranging from 5 mc. to 16.7 mc. with an average dose of 9.6 mc. Aplastic phenomena were marked in 5 cases where the white blood count fell below 4000 and in two cases below 2000. They believed that there was little doubt that in two patients the rapid lethal outcome was due to bone marrow inhibition caused by the radioactive phosphorus. Improvement was noted in only two cases, both of whom received transfusions in addition to isotope therapy.⁸

Multiple myeloma is a rare disease, its incidence having been reported as only 0.03 per cent of all malignant growths,⁹ and it is generally considered to be a disease of later life. Wintrobe¹⁰ states that 80 per cent of the cases occur after the age of 40. Geschickter and Copeland, in a review of 425 cases of multiple myeloma, found that 73 per cent of the patients had an onset of the disease between the ages of 40 and 70, and that it occurred more frequently in males than in females.⁹

The clinical picture of the disease is characterized by pain, often in the ribs, back or sacrum, and the involved areas are sometimes extremely tender to pressure. Pathological fractures of the affected bones and neurological symptoms are very common. The skull is frequently involved. Isolated or multiple tumors may occur and anemia is the usual finding.

The administration of radioactive phosphorus results in its wide distribution throughout the whole body with its greatest initial concentration in rapidly metabolizing tissue such as liver, bone marrow, and tumor tissue, and its subsequent deposition in the bony skeleton.¹¹ Radioactive strontium has been shown to behave similarly to calcium in the body.¹² The biological action of these isotopes on tissue is similar to that of other penetrating radiations, but because of their localization in rapidly growing tissue and in bone, their therapeutic trial in metastatic bone tumors and in multiple myeloma seemed to be indicated. At the outset, it was realized that since only a limited amount of irradiation could be administered to the tumor masses without causing undue damage to the adjacent and normal hematopoietic bone marrow,¹³ much improvement over conventional methods of irradiation could not be expected. The treatment of multiple myeloma with artificially radioactive isotopes was first attempted by us in 1939, and preliminary results from this laboratory were reported in 1941 and 1942 on 11 patients with multiple myeloma treated either with radioactive phosphorus or radioactive strontium or both.^{14, 15} The response of these patients to the radioactive elements was not uniform and seemed to be closely correlated to the condition of the patient at the time treatment was started. In some patients, there was marked relief of pain and at times a restoration to almost

TABLE I
Summary of History of 24 Cases of Multiple Myeloma

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years)			Response to Isotope Therapy	Complications
						Before Isotope Therapy	Usual	Total		
1. (G. A.) *4-6-39	59	F	Backache, root pain; x-rays show diffuse bone involvement	Biopsy of rib; Bence-Jones pos.	X-ray; 9911 r; Coley's toxin	1.0	None	1.2	None	Due to x-ray anemia; required transfusions; received 2000 r additional
2. (C. A.) *10-30-41	48	M	After fall x-ray showed rib fracture and lesion in femur	Biopsy of rib	X-ray; 1800 r	1.2	1.0	2.8	Good	Anemia; leukopenia; required transfusions
3. (D. B.) *8-23-41	45	M	Backache, root pain; x-rays show diffuse involvement	X-ray; sternal pos. 13% myeloma cells; Bence-Jones neg.	None	0.2	None	0.5	None	Anemia; required transfusions
4. (H. B.) *9-11-40	51	M	Pain in back, root pain after fall; x-rays showed fracture T8, 9, 10; lesions in skull and ribs	X-ray; sternal pos. Bence-Jones pos.	X-ray	0.5	6.5	7.2	Good	None
5. (E. E.) *11-13-40	52	F	Pain in back; x-rays showed osteoporosis of spine, ribs	X-ray; sternal pos. Bence-Jones pos.	X-ray; transfusions for severe anemia	1.1	1.6	1.8	Fair	Thrombopenia
6. (G. F.) *9-7-45	65	M	Pain in arm, shoulder, neck; laminectomy with meningitis; x-rays showed bone involvement	X-ray; sternal pos. Bence-Jones neg.	X-ray	1.0	0.3	1.2	None	None

TABLE 1—Continued

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years)			Response to Isotope Therapy	Complications
						Before Isotope Therapy	Useful	Total		
7. (J. H.) *7-18-40	49	F	Pain with rib fracture; x-rays showed diffuse bone involvement	X-ray; Bence-Jones pos.	X-ray; transfusions	1.8	1.0	2.4	None	Anemia; leukopenia more severe; required transfusions
8. (R. H.) *9-1-44	66	M	Slipped and fractured rib and vertebrae; tumor of chest wall	Biopsy of tumor showed plasmocytoma	X-ray; 10,000 r	2.5	2.7	3.0	Slight	None
9. (H. H.) *7-13-44	46	M	Albumin in urine proved to be Bence-Jones; x-ray showed diffuse involvement. Sternal pain	X-ray; Bence-Jones pos.	None	0.5	1.0	1.3	Slight	Anemia
10. (C. J.) *4-14-41	50	F	Upon sitting up in bed fractured left trochanter. Amputation two years later	Biopsy of leg	X-ray; transfusions	7.0	7.25	8.7	None	Anemia; leukopenia; required 35 transfusions
11. (W. K.) *4-28-44	55	F	Pain in arm, chest, shoulder; fractured rib; x-ray showed diffuse involvement	X-ray	None	0.3	0.2	0.5	None	None
12. (M. M.) *9-28-44	38	M	Albumin in urine; weakness; weight loss	Sternal pos. 24% myeloma cells; Bence-Jones pos.	None	0.8	2.9+	2.9+	Slight	Slight anemia
13. (E. R.) *6-7-40	41	M	Backache; albumin in urine; x-rays show diffuse involvement	Sternal pos. Bence-Jones pos.	X-ray	0.9	1.4	1.9	Fair	Anemia; leukopenia; thrombopenia

TABLE 1—Continued

Case No.	Age Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years)			Response to Isotope Therapy	Complications
						Before Isotope Therapy	Useful	Total		
14. (F. R.) *9-16-42	62	F	Pain in arms, neck, shoulders; tumor over sternum; "soft spots" in skull	Sternal pos.	None	—	0.3	1.0		
15. (S. S.) *10-10-44	47	M	Numbness and tingling of hands; sacroiliac pain; pain in left lower thorax	X-ray	None	1.0	0.9	1.8	Slight	None
16. (S. S.) *1-18-39	58	F	Bone pain; x-rays show diffuse involvement	Sternal pos. x-ray	X-ray; 8 transfusions	0.8	3.0	4.0	Good	None
17. (G. W.) *10-23-41	44	F	Pain in spine; root pain; bedridden	Biopsy of ilium	X-ray	3.1	5.7	7.0	Fair	Aplastic anemia; purpura; required transfusions
18. (F. W.) *9-6-41	54	M	Pain in back; x-ray showed tumor of vertebrae	X-ray; sternal pos.	X-ray; transfusions	3.0	1.0	3.6	Slight	Aplastic anemia; purpura; hemorrhage; required transfusions
19. (G. K.) *2-15-43	58	M	Extreme fatigue; poor vision, headache and vertigo; pain in lower dorsal spine and chest	X-ray	None	1.5	3.6	5.0	Slight	Polycythemia; neuro-nitis
20. (E. W.) *10-12-48	62	M	Backache, 4 months' duration; fatigue 9 to 10 months	X-ray lesions in skull, vertebrae, ribs, Bence-Jones pos.; sternal marrow	Deep x-ray to L 1.		0.4	0.5		Anemia

TABLE 1—Continued

Case No.	Age at Onset	Sex	Pertinent History	Method of Diagnosis	Previous Therapy	Duration of the Disease (Years)			Response to Isotope Therapy	Complications
						Before Isotope Therapy	Useful	Total		
21. (L. K.) *9-17-47	54	M	Pain in shoulder; then mass	Biopsy of acromial process, L. scapula; x-ray lesions 11th, 12th dorsal vertebrae, L. radius and ulna; pos. Bence-Jones; sternal marrow	None	0.6	0.7	0.7	None	Anemia; hemorrhage from biopsy wound; death 8 mos. after first symptoms
22. (R. T.) *11-30-48	29	M	Pain in L. sacroiliac region, intermittent 3 years; swelling over eye	X-ray destructive lesions in L. ilium, R. clavicle, skull, R. 12th rib; biopsy of R. 9th and 12th ribs	X-ray	3.0	3.0	—	None	Anemia
23. (B. C.) *1-13-49	65	F	Paresthesias of hands, feet; weakness of legs, incoordination, 8 months later	X-ray myeloma of ribs, acetabulum; sternal and iliac marrow	X-ray to spine	0.8	0.9	1.1	Slight	Cord compression
24. (E. B.) *1-16-48	50	F	Pain in arms and legs	Bence-Jones pos.; increased plasma cells in sternal marrow	None	—	2.4	—	—	Polycythemia; diabetes mellitus

* Indicates date first seen by us.

normal activity. The present series of 24 patients (14 men and 10 women) includes in summary all previously reported cases from this laboratory.^{14, 15}

The ages of onset of multiple myeloma in this series of patients ranged from 29 to 66 years with the average at 51.9 years. Fifteen of the patients were over 50 years old at the onset of the disease. Only 2 of the patients are still living (Cases 22 and 24). The clinical and hematological data on all patients are summarized in tables 1, 2 and 3.

Fifteen of the patients had received x-ray therapy before they came under our observation. Anemia, in some instances probably due to previous x-ray therapy, was noted in 11 cases prior to the beginning of treatment with radioactive isotopes, and anemia of variable severity developed in 10 of the other patients while they were under our observation. Leukopenia was noted in four cases when first seen by us, and in three additional cases there was a marked fall in the white blood cell count during treatment with P³².

TABLE II
Hematologic Data in 24 Cases of Multiple Myeloma

First horizontal column in each case signifies blood count when first seen; second column after therapy had been completed. (This period of time does not necessarily correspond to the duration of treatment as noted in table 3. The time elapsed between blood counts here is actually the time from the first blood count to the final significant blood count after therapy had been completed and had had time to become effective.) Case 22 is a living patient and therapy has not yet been completed. Case 24 is a living patient, but no isotope therapy has been given her at this writing.

Case No.	Elapsed time (months)	Hemoglobin grams %	RBC $\times 10^6/\text{mm}^3$	WBC $\times 10^3/\text{mm}^3$	Platelets $\times 10^3/\text{mm}^3$	Poly. Series %	Lymphocyte %	Mono-cyte %	Plasma %
1	0	10.2	3.36	7.05	240	86	5	9	
	1.5	7.5	2.36		190				
2	0	12.4	4.41	6.35	89	56	31	13	
	12	12.5	2.98	2.65		57	42	1	
3	0	13.4	4.39	6.7		43	54	3	
	6	anemia							
4	0	14.2	4.32	9.2		45	53	2	
	80	10.2	3.85	11.75		63	31	6	
5	0	8.5	2.75	4.0	160	68	26	5	1
	4.5	7.8	2.39	4.2	45	68	23	7	2
6	0	7.6	2.52	6.4	220	66	30	4	
	2	10.0	3.77	8.9		78	18	4	
7	0	9.9	3.1	10.4		72	22	6	
	7	5.4	1.74	1.6	18	64	33	3	
8	0	12.2	3.65	5.8	310	73	15	12	
	1.5	10.4	3.11	7.0	95	66	30	4	
9	0	16.9	5.6	15.0	365	71	29		
	9.5	9.3	2.95	7.45	120	86	11	3	
10	0	9.0	3.6	7.45	115	64	26	10	
	5	5.9	2.14	4.4	275	66	30	4	

TABLE II—Continued

Case No.	Elapsed time (months)	Hemoglobin grams %	RBC $\times 10^6/\text{mm}^3$	WBC $\times 10^3/\text{mm}^3$	Platelets $\times 10^3/\text{mm}^3$	Poly. Series %	Lymphocyte %	Monocyte %	Plasma %
11	0	9.0	2.46	8.2		66	26	8	
	1	8.0	2.65	8.8		75	23	2	
12	0	11.9	4.53	7.8	315	34	63	3	
	4	7.0	3.1	5.3	235	48	43	9	
13	0	13.7	4.3	4.57	400	37	63		
	11	4.7	2.03	0.85	6	34	55	10	1
14	0	7.2	2.34	11.1	47	60	36	4	
15	0	10.2	3.57	29.95	200	64	27	9	
	9	11.9	3.02	12.6	190	39	53	8	
16	0	6.9	2.42	5.05		63	30	7	
	37	11.0	3.87	4.8	290	67	23	10	
17	0	10.9	4.62	7.75		73	23	4	
	46	4.3	1.48	5.9					
18	0	6.2	2.5	2.0		76	16	8	
	6	9.0	3.9	1.9					
19	0	15.8	6.18	14.5	440	65	31	4	
	7	15.6	4.96	16.4		72	24	4	
20	0	11.0	3.22	4.35	83	72	17	10	1
21	0	10.3	3.88	7.2	220	60	31	4	5
	1	10.4	2.99	6.85		67	25	8	
22	0	13.0	4.44	7.25	240	68	24	4	
23	0	17.5	4.95	15.0	380	78	15	7	
24	0	14.0	5.10	11.3	370	63	36	2	

Treatment with radioactive isotopes was undertaken in all but three cases (Cases 14, 20 and 24). Case 14, a white female, age 62, had marked bone changes, severe anemia, evidence of kidney damage and was treated symptomatically. Case 20, a white male, age 62, died shortly after he was first seen by us and before isotope therapy could be started. The third patient (Case 24), a 50 year old female of Spanish origin, has, in addition to multiple myeloma, polycythemia and diabetes mellitus, and no treatment has as yet been given her.¹⁶ Cases 19 and 23¹⁶ also had this associated picture of polycythemia and myeloma. Of the 21 patients who were treated with radioactive isotopes, nine received combined P^{32} and Sr^{90} treatment, 11 were treated with P^{32} alone, and one (Case 22) received only colloidal radioactive yttrium (Y^{90}).

RESULTS OF THERAPY

Seven of the 21 cases were not definitely benefited by treatment with P^{32} or Sr^{90} or both (Cases 1, 3, 6, 7, 10, 11 and 21). In five of these cases

TABLE III
Analysis of Dose Schedule of Pa, Sr⁸⁵ and Y⁹⁰. All doses are intravenous unless specified

Case No.	Amount Pa per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Amount Sr ⁸⁵ per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Amount Y ⁹⁰ per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Total Duration Treatment (days)
1	7.6 -8.0*	14	2	15.5	14											14
2	0.4-1.4 1.0-5.0*	3-57	18 6	26.1 (14.8 11.3*)	251											251
3	1.5-1.6 5.0*	2-6	2 1	8.1 (3.1 5.0*)	9	0.14-1.9	2-3	4	3.9	7						13
4	1-3 5-8*	7-480	21 9	103.0 (84.5 18.5*)	2390											2390
5	6.0*	42	4	24.0	120											120
6	1.1 -2.1	7-18	4	6.9	42											42
7	5.0*	39-50	3	15.0	90	1.0 -2.0	7	6	8.95	42						180
8	0.7 -1.2	3-7	5	4.8	21	0.2 -0.3	2-14	4	0.8	21						44
9	0.3 -1.6	6-94	9	8.6	240	0.3	none	1	0.3	1						240
10	4.0 -4.8*	14-15	4	16.8	42											42
11	1.1	none	1	1.1	1	0.7	none	1	0.7	1						7
12	0.54-1.2	9-49	5	4.3	86	0.3 -0.8	2-5	4	1.9	14						86
13	2.6 -6.0 5.0*	17-42	2 3	23.6 (8.6 15.0)*	291	0.6 -1.6	7-33	5	4.7	56						291

TABLE III—Continued

Case No.	Amount in per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Amount S ₉₉ per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Amount S ₉₉ per Dose (mc)	Interval between Doses (days)	Number of Doses	Total Dose (mc)	Duration Treatment (days)	Total Duration Treatment (days)
14	none					none										
15	0.5-1.5 0.3*	16-52	9 1	6.8 (6.5 0.3*)	270	0.55	7	2	1.1	7						270
16	1.0-6.0*	7-210	16	62.8	1130											1130
17	5.0*	360	2	10.0	360	0.6-1.0	2-4	6	5.3	14						1350
18	2.0-3.0 6.0*	15-57	2 2	17.0 (5.0 12.0*)	174											174
19	0.33-7.3 2.42*	3-85	9	20.98	201											201
20	none					none										
21	1.0	2-11	4	4.0	17											17
22						Y ₉₉ 3.0-4.0	9-12	3	10.0	22						22
23	1.0	7-38	6	6.0	66	none										66
24	none															

* oral

(Cases 1, 3, 6, 11 and 21) the patients were first seen in a very advanced stage of the disease, so that probably no treatment of any kind would have been beneficial. Case 7 had a severe anemia when first seen by us, and treatment with fairly large doses of isotope was unsuccessful. In Case 10, seven years after the first symptoms appeared, widespread metastases were noted, although the initial lesion, localized in the left femur, had been solitary for many years. This patient, when first seen by us, had a moderate anemia, and no benefit resulted from isotope therapy. Case 22, treated with colloidal radioactive yttrium, was not benefited by this isotope.

In eight other cases the benefit from treatment with radioactive isotopes was rather questionable (Cases 8, 9, 12, 15, 17, 18, 19 and 23). Case 8, a physician 55 years of age, started treatment with P^{32} two and a half years after the date of onset, felt "much better" during the treatment with P^{32} and Sr^{90} , but the progress of the disease was not influenced and the patient died three months after beginning therapy. Case 12 had no bone changes at the onset of treatment, and the therapeutic response was minimal. Case 15 started treatment relatively late and felt better for a short time, but his disease progressed and the patient became bedridden. Treatment in another patient (Case 17) was followed by temporary improvement, but because of the development of a severe anemia which required transfusions, therapy had to be discontinued. Cases 9 and 18 had slight symptomatic improvement, but the progress of the disease was not markedly influenced. Case 19 is interesting in that the patient was thought to have polycythemia vera when therapy with P^{32} was instituted. Later, shortly after the beginning of therapy with P^{32} , the patient developed definite lesions of the vertebrae and eventually died with the picture of multiple myeloma which may have been present from the very beginning in view of the rare but definite occurrence of polycythemia and multiple myeloma in the same patient.¹⁰ During the period of about three years prior to his death, the patient received considerable benefit from the P^{32} therapy, and the progress of the multiple myeloma may have been temporarily inhibited. In Case 23, there was some temporary improvement in the subjective symptoms but no clear-cut effect on the progress of the disease.

In five patients (Cases 2, 4, 5, 13 and 16) the results of treatment with radioactive isotopes were relatively satisfactory. Case 2, described by us in 1942,¹⁵ had an excellent response for about one year. At the start of treatment, his legs were atrophied, he required crutches for any movement, and he was unable to walk or work. After two months of treatment, his improvement was so marked that he was able to walk without crutches and had resumed his work. However, this remission was of only approximately a year's duration, and at the end of that time the patient was confined to bed with a terminal mild anemia and leukopenia which interfered with the planned treatment and prevented further radioactive isotope therapy.

Case 4 (H. A. B.) was especially remarkable since the duration of the disease, extending over a period of more than seven years, was unusually

long and because the patient did exceedingly well under treatment with radioactive phosphorus. H. A. B., a 52 year old physician, slipped in February, 1940, and developed severe back and root pain. In May, 1940, x-ray revealed compression fractures of T 8, T 9, and T 10 with osteoporosis and radiolucent areas in the ribs, pelvis and skull. When he was first seen by us in September, 1940, physical findings were essentially negative. The blood count was normal with the hemoglobin 103 per cent, red blood cells 4,320,000, white blood cells 9200 with 53 per cent lymphocytes. The urine was negative for Bence-Jones protein. Sternal biopsy revealed the presence of many myeloma cells, and oral P^{32} therapy was started. The total dosage of 103 mc. over a period of six and one-half years was as follows:

1940	33.0 mc.
1941	26.5 mc.
1942	13.0 mc.
1943	no treatment
1944	7.5 mc.
1945	4.5 mc.
1946	14.5 mc.
1947	4.0 mc.

In 1940, the patient was in bed for several months because of severe girdle pain, but by the next year he had improved sufficiently to drive his car and go hunting and fishing. He remained well until 1945 when definite progression of the disease was noted, followed a year later by a mild degree of anemia, extensive involvement of the skull, and involvement of the mandible from which the patient suffered considerably. Treatment with stilbamidine, instituted by Dr. Snapper, produced no marked effect, and the patient deteriorated steadily until his death four months later.

Case 5, a white female age 50, had a severe anemia and after each dose of P^{32} a marked diminution of the platelet count occurred (from 160,000 to 45,000). However, after treatment the patient was able to get about easily and pain was relieved. In spite of pancytopenia, the rate of progress of the disease was definitely diminished and pain was relieved more effectively than by x-ray or opiates.

In Case 13, the benefit obtained by P^{32} and Sr^{90} was only temporary. The patient complained of severe pain in the back which had become increasingly severe up to the time of treatment. During the treatment with P^{32} and Sr^{90} , these pains disappeared completely. However, at the same time severe anemia, leukopenia and thrombopenia developed and the patient ultimately died despite many transfusions. Bone marrow biopsy, performed shortly before death, revealed hypoplasia of the marrow elements.

Case 16 was bedridden for almost a year. Treatment with radioactive phosphorus was followed by marked improvement, so that the patient was able to be up and about. It seemed almost unbelievable that this patient, who had been in extreme pain almost constantly and had been unable to move unaided in bed a year previously, had become pain free and was able to resume her previous occupation as a teacher. This remission lasted for one

and one-half years after which the patient again became bedridden because of collapsed vertebrae and fractured ribs, and she died in coma. The result, although temporary, was quite striking.

Of the patients who were treated and are now dead, the length of life after onset of the disease ranged from six months to nearly nine years, with an average length of life of approximately three years after onset. This is slightly longer than in previously reported series^{3,9} but not markedly so.

DOSAGE

At the beginning of treatment with radioactive phosphorus, large single doses at short intervals of two to three days were tried in order to build up a high radiation level (table 3). Later smaller weekly or bi-weekly treatments were given. More positive knowledge about the dosage and frequency of treatment is, of course, highly desirable, but we cannot at the present time recommend any precise line of treatment. The general condition of the patient and hemogram must be considered at the time the patient is first seen and treatment started. The dosage must be individualized and the patient carefully followed with special attention directed to the state of his hematopoietic system. One millicurie of P^{32} intravenously once or twice a week for four to six weeks, or about 5 to 10 mc. per course, is suggested. After three to four months, if the blood picture is satisfactory, more radiophosphorus may be given if it is indicated.

The dosage and frequency of therapy of the nine patients who were treated with radioactive strontium are shown in table 3. Inasmuch as Sr^{90} treatment was used in a limited number of cases, and since P^{32} was usually administered also, it is difficult to evaluate the treatment of multiple myeloma with Sr^{90} from these observations. There was no evidence that the combination of Sr^{90} and P^{32} proved more effective than P^{32} alone.

COMMENT

The results of our treatment of multiple myeloma with these radioactive elements were not markedly better than those obtained with x-ray and with stilbamidine.^{1,3} Radiosensitive cases may be influenced equally well by x-ray or by artificially radioactive elements, although it is not certain that we are influencing the course of the disease by any type of radiation. In view of the fact, however, that the radioactive isotopes are more easily applied than x-ray therapy and have no side effects, this treatment is worth trying in multiple myeloma. The symptomatic improvement and the relief of pain obtained by the use of artificially radioactive isotopes were in some cases so striking that the favorable effect of this type of therapy seemed definite. At times, it seemed to us that a combination of isotope therapy plus x-ray was more effective in causing improvement. Likewise, it seems unlikely that radiostrontium will be a valuable therapeutic agent because of

its selective deposition and long half life (55 days), and since, as in the case of P^{32} , the bone marrow is constantly being irradiated during this period. Thus, an amount of radiostrontium sufficient to destroy tumor cells would produce damaging effects on the normal marrow components before destruction of the neoplastic lesions could be achieved. More intensive work with strontium 89 in the treatment of myeloma and other bone lesions is necessary for its evaluation as a therapeutic agent. Similarly, combination therapy with P^{32} or Sr^{90} , the diamidine compounds, and urethane would seem to be a worthwhile approach to the treatment of this disease which has thus far proved to be such a discouraging problem. Finally, radioactive stilbamidine, now being studied in this laboratory, may be of therapeutic value because of its combined chemotherapeutic and possible selective irradiation effects.* There is little doubt in our minds that radiation is of some benefit in myeloma, and if it can be delivered to the plasma cells by some selectively localizing radioactive compound, considerable improvement in the results with an increase in comfortable life and life expectancy can be anticipated. But, until such a satisfactory therapeutic agent is discovered, the prolongation of useful life must remain an important consideration in the treatment of multiple myeloma.

CONCLUSIONS

1. Radioactive phosphorus and radioactive strontium have been used as therapeutic agents in multiple myeloma. Improvement was noted in some cases. The average length of life after the onset of the disease in this group of patients was approximately three years.

2. These isotopes are valuable in producing whole body background irradiation which may in itself afford some relief. The combination of isotope therapy and x-ray or stilbamidine or urethane is suggested.

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A PHONOCARDIOGRAPHIC STUDY OF APICAL DIASTOLIC MURMURS SIMULATING THOSE OF MITRAL STENOSIS *

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It has been known for a long time that patients with an enlarged left ventricle and auricle and a normal mitral orifice may present a diastolic murmur at the apex, simulating that of mitral stenosis. In particular, this diastolic murmur has been described in patients with: (a) hyperthyroidism; (b) congenital heart disease, especially septal defects; (c) mitral insufficiency and no appreciable stenosis; (d) aortic insufficiency; (e) hypertensive or coronary heart disease; (f) adhesive pericarditis.

With a few exceptions, to be quoted later, the above studies were based upon clinical auscultation. For this reason we thought it interesting to start a series of observations, based upon graphic studies of the heart sounds and murmurs and a correlation of these with all the other clinical and laboratory data.

PREVIOUS STUDIES

There are numerous studies on diastolic apical murmurs which simulate mitral stenosis. Three important works should be quoted as they mark three stepping stones in the progress of our knowledge of functional diastolic murmurs:

(a) The classical study of Austin Flint¹ on the functional apical diastolic murmur which may be heard in aortic regurgitation.

(b) The study of P. D. White² on apical diastolic murmurs, due to an enlarged left ventricle, in pericardial or hypertensive heart disease.

(c) The study of Bland, Jones, and White³ on the diastolic murmur of rheumatic heart disease without mitral stenosis.

Following a series of interpretations which were not supported by evidence and which sometimes disagreed with known facts of cardiac physiology, the last and most acceptable interpretation of the diastolic apical murmur is that of P. D. White²: In the presence of a normal mitral orifice, any increase in the amount or speed of the blood flowing through the orifice may cause whirlpools and thence murmurs. This may take place in certain cases of hyperthyroidism, in certain patients with enlarged left auricle and

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ventricle (mitral regurgitation), and in cases with tremendous enlargement of the left ventricle (aortic insufficiency, hypertensive and coronary heart disease, congestive failure) or disturbed function of the left ventricle (adhesive pericarditis).

A few graphic studies were published in the last 15 years. The following should be quoted:

Bramwell⁴ investigated the tracings of heart sounds in Graves' disease, with and without heart block, and reached the conclusion that "The similarity between the first heart sound in hyperthyroidism, in certain athletes, in some cases of congenital heart disease, and in some patients with high blood pressure and the first heart sound and presystolic murmur of mitral stenosis may be due to an increased velocity of the blood flow through the mitral orifice when the auricular muscle is hypertrophied."

Taquinì, Massell, and Walsh⁵ demonstrated, by means of graphic tracings, that the diastolic extra-sound or rumbling murmur of early rheumatic mitral disease actually is due to a gallop sound.

This study was extended by one of us (Luisada) to later stages of rheumatic heart disease in adults.^{6,7} Phonocardiograms showed that ventricular gallop, auricular gallop, summation gallop, or even the combination of a ventricular plus auricular gallop (train wheel rhythm) may give the impression of a rumbling diastolic murmur on auscultation.

A graphic study of the apical murmurs in aortic insufficiency was also published by one of us (Luisada).⁸ In a series of cases, apical diastolic murmurs which had been interpreted as Austin Flint murmurs were due to either a gallop sound or a crescendo-type of the first sound without any evidence of a valvular murmur. A similar conclusion was later reached by Evans.⁹

The particular changes of the first heart sound, which may start with some delay when compared to the QRS complex of the electrocardiogram, have been studied by Luisada¹⁰ and by Cossio and co-workers.^{11,12} This abnormality of the first sound is usually present in mitral stenosis but occasionally may simulate upon auscultation the existence of a presystolic murmur even without stenosis of the mitral valve.

In a recent contribution, proof was given that, in the presence of a calcified or senile mitral valve, the auricular contraction may be followed by a murmur without mitral stenosis (Rytand).¹³

The cases reported by Weinstein and Lev¹⁵ have furnished anatomical proof of the mechanism of apical diastolic murmurs simulating mitral stenosis. The cases of Robinow and Harper,¹⁶ even though not correlated by graphic tracings, add to the number of those with a "relative" mitral stenosis.

MATERIAL AND TECHNIC

The cases reported in this paper are the most outstanding from a collection of over 1500 phonocardiograms recorded in 910 cases and do not

represent a recent selection. On the contrary, every case in which the clinical diagnosis of mitral stenosis was made and subsequently disproved by the phonocardiogram, the later course, or a postmortem examination, was set aside for further use. In this way, 62 cases were collected within seven years by one of us (Luisada). Out of this group, a further selection was made and 13 cases were further studied and are reported here. The selection of cases was made either because of the striking simplicity with which the phonocardiogram proved that the diagnosis was incorrect or because the phonocardiogram seemed to confirm the diagnosis of a valvular lesion while subsequent data proved that the patient had no mitral stenosis.

The patients were studied with the electrocardiograph, the phonocardiograph (a Sanborn Stethocardiette was used), and the x-ray. Some of the cases were hospital patients and were discussed by the hospital and consulting staffs of the Beth Israel Hospital and Boston City Hospital; the others were private patients, seen in consultation with various physicians.

CASE REPORTS

Auricular and First Sound Simulating the Murmur of Mitral Stenosis

Case 1. A man of 85. At the age of 55, he could not obtain insurance because of a "heart murmur." He had been treated since the age of 64 by the same physician for "mitral stenosis." He had been digitalized for the past 10 years and had repeated attacks of fainting.

There were signs of chronic congestive failure. The pulse was irregular. Auscultation revealed a presystolic rumble, simulating that of mitral stenosis. The

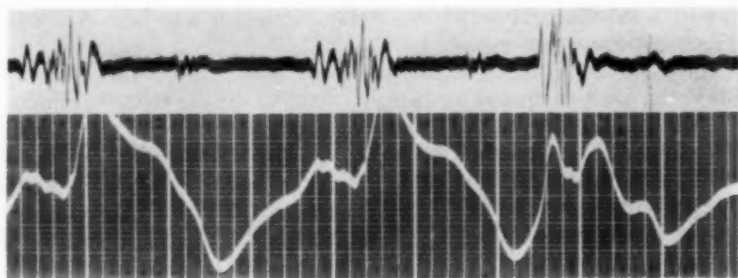


FIG. 1. *Case 1.* Phonocardiogram and cardiogram recorded at the apex. Senility, myocardial fibrosis, premature contractions. Loud and prolonged auricular sound; prolonged phase of high vibrations of the first sound; poor intensity of the second sound. Arrhythmia due to premature beats.

electrocardiogram showed sinus rhythm with frequent auricular and ventricular premature beats.

The phonocardiogram revealed that there were no murmurs. The first sound presented a prolongation of the phase of high vibrations and a loud auricular sound, consisting of two low-pitched vibrations. The cardiogram showed a high auricular wave (figure 1).

It is apparent that the combination of various elements, the loud and prolonged auricular sound, the abnormal first sound, and the arrhythmia gave rise to an incorrect clinical diagnosis.

Case 2. A married woman of 37 with no knowledge of previous disease. The patient complained of precordial pain, not typical of angina pectoris. The pulse was rapid (100); the blood pressure, normal. The heart was of normal size and there were no thrills. Clinical auscultation revealed a presystolic murmur and a short systolic murmur. The electrocardiogram was normal; roentgenology revealed a normal heart.

The phonocardiogram (figure 2) revealed an auricular sound made up of three low-pitched serial vibrations. The first sound presented a prolongation of the phase of high vibrations, these succeeding each other as a crescendo. There was a short, early systolic murmur. No opening snap of the mitral valve and no diastolic murmur were observed.

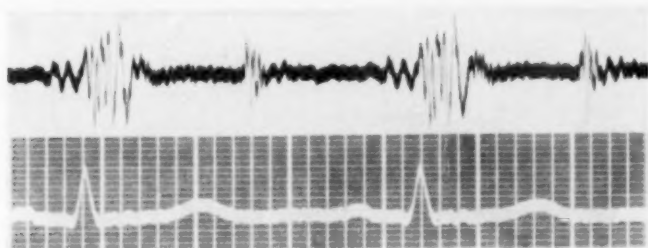


FIG. 2. *Case 2.* Phonocardiogram of a 37 year old woman without valvular defects. Visible auricular sound with four vibrations; the first sound is prolonged and has a crescendo type of vibrations. Small vibrations of a systolic murmur are present in the first part of systole.

The general conclusion was that no valvular defect existed. The patient was suffering from a complex endocrine disorder, partly connected with an early, impending menopause. The abnormal types of the auricular sound and of the first sound explain the auscultatory impression of mitral stenosis.

Bundle Branch Block and Fibrosis of the Mitral Valve Simulating Mitral Stenosis

Case 3. A woman of 67, admitted to a Home for the Aged. The clinical diagnosis was "mitral stenosis and auricular fibrillation," based on a loud apical systolic murmur, a diastolic rumble, a split second pulmonic sound, and a marked irregularity of the pulse. The electrocardiogram confirmed the existence of auricular fibrillation and revealed the existence of bundle branch block (figure 3a).

The phonocardiogram showed a loud gallop sound at the apex, following the second sound. It further showed that whenever there was a short diastole, low-pitched diastolic vibrations were visible; the second sound was split over the mid-precordium because of the bundle branch block (figures 3b and c). The arrhythmia, the existence of a systolic murmur, the splitting of the second sound, the gallop, and the occasional diastolic vibrations combined to simulate the auscultatory picture of mitral stenosis.

It was concluded that the systolic murmur and the occasional diastolic vibrations were due to a functional mechanism and possibly to fibrosis of the mitral valve. The ultimate diagnosis was: arteriosclerotic heart disease with myocardial and valvular fibrosis.

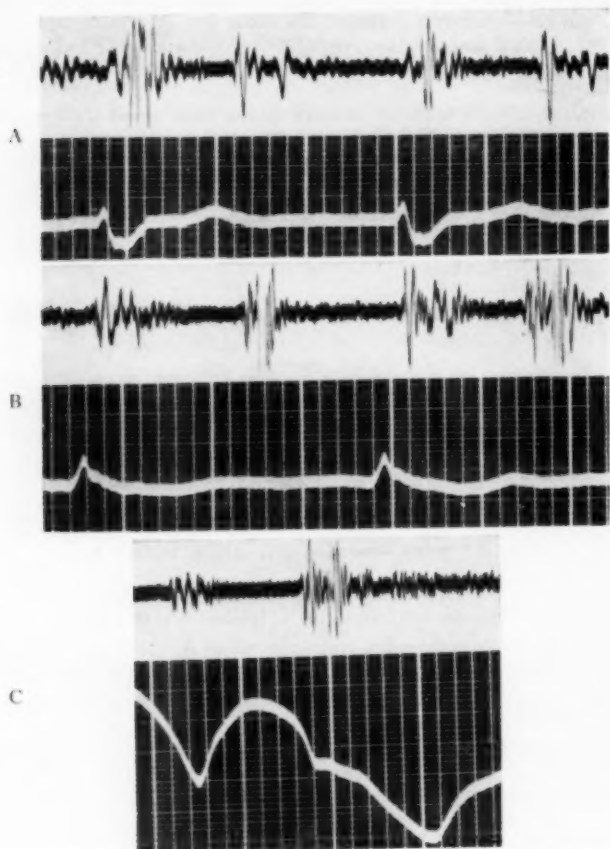


FIG. 3. Case 3. Senility, fibrosis of the myocardium and of the cardiac valves, intraventricular block.

(A) Phonocardiogram at the apex and electrocardiogram. Systolic murmur, ventricular gallop, diastolic vibrations visible at the beginning of the tracing.

(B) Phonocardiogram recorded over the pulmonary area and electrocardiogram. Systolic murmur, prolonged first sound, split second sound.

(C) Phonocardiogram over the third left interspace and carotid tracing. The first phase of the second sound coincides with the incisura showing that there is a right bundle branch block.

Adhesive Pericarditis Simulating Mitral Stenosis

Case 4. A man of 53. The patient had a sudden attack of precordial pain and was brought to the Hospital. Dull heart sounds and a precordial friction rub were heard but the electrocardiogram was normal. Diagnosis of acute pericarditis was made. A few weeks later, a systolic murmur and an early diastolic murmur were heard at the apex and the possible existence of mitral stenosis was discussed. The phonocardiograms showed that no diastolic vibrations were present. Irregular, high-pitched vibrations were present during the whole of systole; a group of four high-pitched vibrations was present in the second half of systole, coinciding with the peak of the T wave (figure 4). This represented the graphic expression of a *late systolic snap* which was mistaken for the second sound, while the actual second sound, with the few systolic vibrations preceding it, was mistaken for a diastolic murmur.

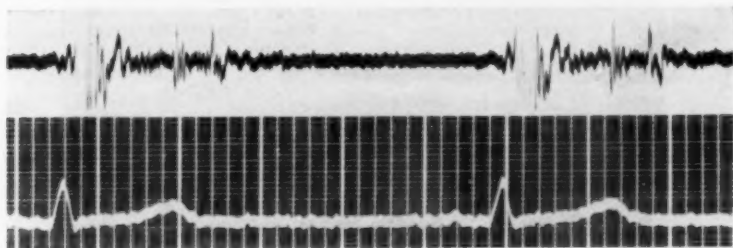


FIG. 4. Systolic murmur and late systolic snap due to pericardial adhesions. Upon auscultation, the snap was mistaken for the second sound, while the second sound was thought to be a diastolic murmur.

The ultimate diagnosis was: Systolic murmur and systolic snap caused by pericardial adhesions.

Case 5. A 12 year old boy. The patient was studied two years before the last entry. At that time a late-systolic, musical murmur was heard at the apex and the second sound was followed by a loud snap (figure 5a). The second sound was split over the pulmonic area (figure 5b).

The phonocardiogram confirmed these facts and seemed to confirm the diagnosis of mitral insufficiency and stenosis in spite of the fact that the murmur was noted only in late systole. The apical cardiogram did not give clear results and the early diastolic snap was interpreted as an opening snap of the mitral valve. Subsequently, the diagnosis of adhesive pericarditis was made and the patient was subjected to the removal of part of three ribs in the precordial area.

Examined one year after the operation, the heart presented no murmurs but there was a rumble during diastole. The cardiogram and the phonocardiograms were recorded simultaneously by applying the funnel over the soft part of the chest and in direct contact with the pulsating heart. The cardiogram was atypical. The phonocardiogram revealed, in addition to the two normal heart sounds, a loud opening snap of the mitral valve, a ventricular gallop, and an auricular gallop (figure 5c). The succession of these diastolic extra-sounds created the impression of a diastolic rumble.

The incorrect diagnosis made during the first entry was due to the systolic murmur and to the diastolic extra-sound, probably due to a split second sound.

Mitral Insufficiency and Gallop Sounds Simulating Mitral Stenosis

Case 6. This 30 year old married woman, with a history of repeated sore throats, complained of palpitation and occasional precordial pain. Physical examination revealed a faint systolic murmur and an indistinct diastolic rumble.

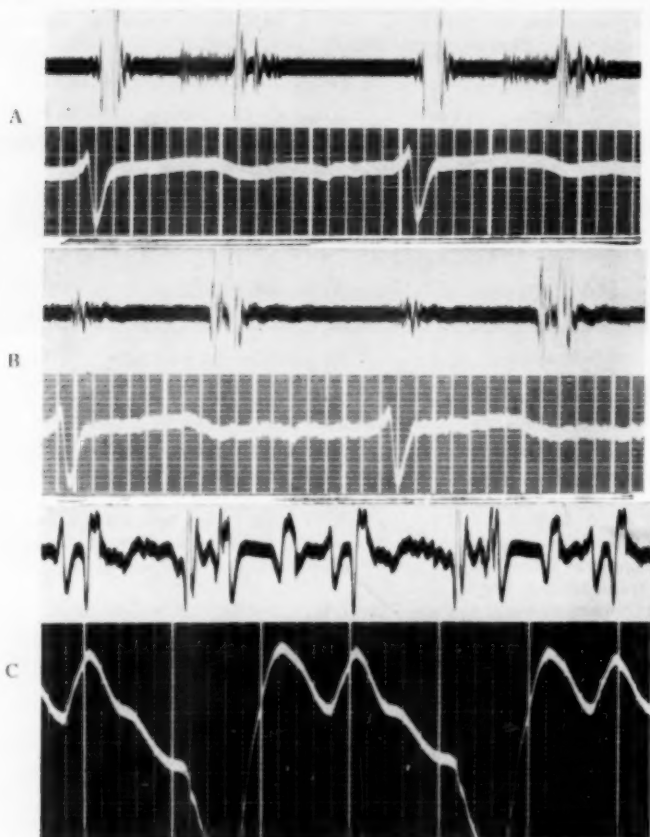


FIG. 5. Phonocardiograms of a boy recorded with a two year interval: (A) and (B) one year before operation for adhesive pericarditis; (C) one year after operation.

(A) Electrocardiogram and phonocardiogram at the apex. Late-systolic murmur and reduplication of the second sound.

(B) Electrocardiogram and phonocardiogram over the pulmonic area, split second sound.

(C) Cardiogram and phonocardiogram simultaneously recorded over the soft, operated, precordial area.

The phonocardiogram revealed that the apical tracing presented a ventricular gallop during diastole which was louder than the second sound while an auricular sound also was present. The vibrations of the systolic murmur were of small amplitude and were revealed better by the logarithmic microphone; there was no opening snap of the mitral valve and no diastolic murmur (figure 6A).

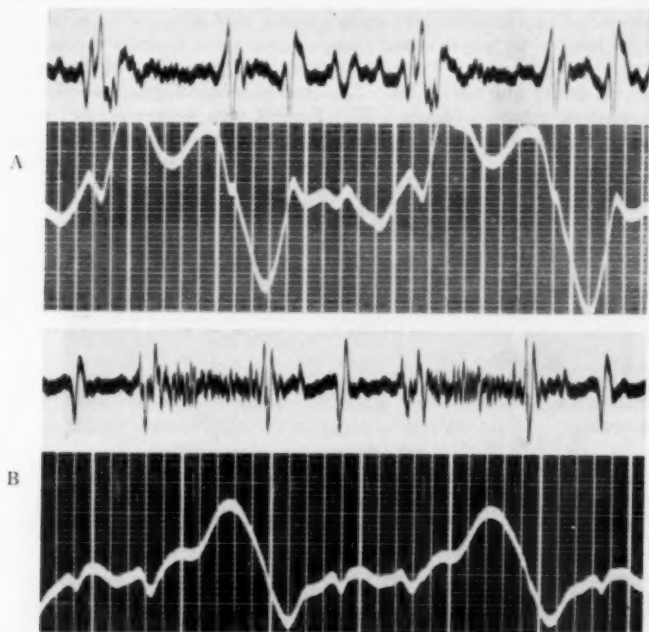


FIG. 6. Two cases of rheumatic heart disease with mitral regurgitation; gallop sounds simulate mitral stenosis. Phonocardiogram and cardiogram.

Case A. Faint systolic murmur, ventricular gallop, auricular sound. The cardiogram presents a second plateau in diastole.

Case B. Loud systolic murmur and ventricular gallop.

The complex of clinical, electrocardiographic, roentgenological, and phonocardiographic data led to the diagnosis of moderate mitral insufficiency and permitted the exclusion of mitral stenosis.

Case 7. A 50 year old man with a history of pulmonary tuberculosis. The patient complained of epigastric pain, palpitation, and dependent edema. The heart was very large; it presented a loud systolic murmur and a diastolic snap which was interpreted as an opening snap of the mitral valve. The electrocardiogram showed a P-R interval of 0.24 sec. The phonocardiogram showed the vibrations of a long, continuous, systolic murmur at the apex and mid-precordium while the snap was recognized as a ventricular gallop (figure 6B).

The final diagnosis was: rheumatic heart disease, mitral regurgitation.

Auricular Flutter Simulating Mitral Stenosis

Case 8. A man of 53, who had occasional precordial pain and palpitation for the past five years. Moderate hypertension and "heart trouble" had been diagnosed. On observation, he was in a state of congestive failure with a blood pressure of 160/100 mm. Hg; the pulse was 130, regular and alternating. Auscultation of the heart revealed a presystolic rumble. The electrocardiogram indicated auricular flutter.

The phonocardiogram showed the existence of a loud presystolic murmur (figure 7A). On the basis of the physical and phonocardiographic findings, the diagnosis of mitral stenosis was advanced. The patient received a large dose of digitalis which transformed the flutter into fibrillation. A second phonocardiogram revealed a short, very loud, diastolic murmur (figure 7B). Treated with quinidine, the patient reverted to a normal sinus rhythm. A third phonocardiogram (figure 7C) showed a

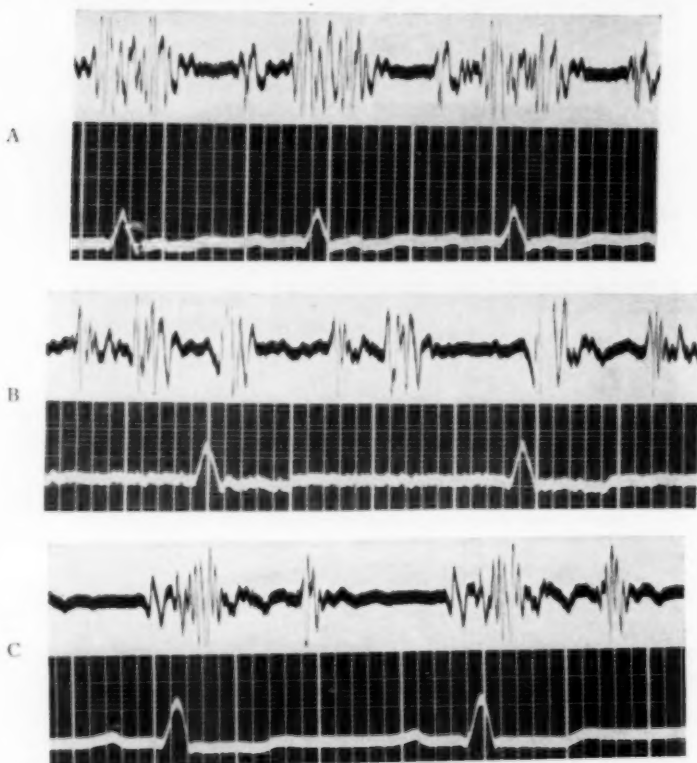


FIG. 7. Three phonocardiograms recorded at brief intervals on the same patient.

The first was recorded during an attack of auricular flutter; the second was taken two days later, after transformation of the flutter into fibrillation by means of digitalis; the third was recorded 10 days after the second, when the patient again had sinus rhythm after the administration of quinidine. A diastolic rumble is visible in tracings (A) and (B) while an auricular gallop is visible in tracing (C).

loud auricular gallop, a prolonged first sound, and no diastolic murmur. This allowed us to attribute the diastolic murmur previously observed to a functional mechanism, causing large vibrations in the sound tracings because of severe enlargement of the heart and a deep chest.

The patient was able to continue normal physical activity for one year subsequent to the above observations. At the end of this period, the patient had a coronary occlusion and died after one week.

Auricular Sound Simulating Mitral Stenosis In Aortic Insufficiency

Case 9. The patient, age 26, had aortic regurgitation of undetermined etiology. Auscultation at the apex revealed the existence of a short, harsh, presystolic murmur "in crescendo" and a soft systolic murmur.

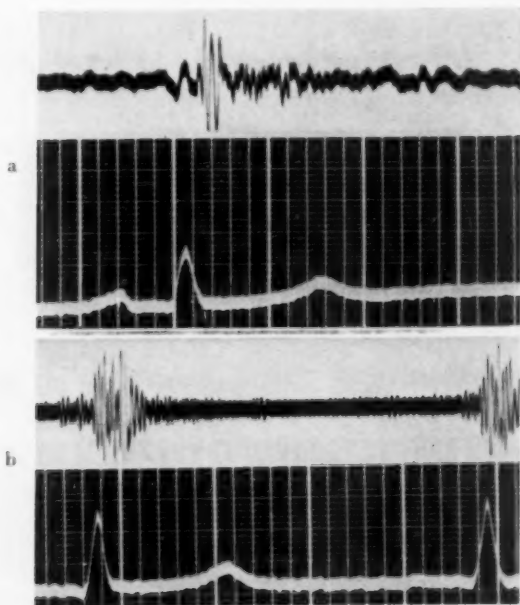


FIG. 8. Apical phonocardiograms recorded by means of the stethoscopic (a) and logarithmic (b) microphones in a patient with aortic insufficiency and a clinical impression of a presystolic murmur.

A phonocardiogram, recorded at the apex with both the stethoscopic and logarithmic microphones, showed a rather high auricular sound, causing a few high-pitched vibrations which, added to those of the first sound, transformed the latter into a crescendo type of murmur (figure 8).

The conclusion was: aortic regurgitation, auricular gallop. Mitral stenosis was excluded on the basis of the phonocardiogram.

Austin Flint Murmur

Case 10. A patient, age 54, with the clinical diagnosis of aortic insufficiency and aortitis of luetic etiology; hypertension. The patient was examined repeatedly during two years.

The apical phonocardiogram recorded during the first examination revealed a high auricular sound, a curiously distorted type of first sound, and a systolic murmur. After repeated episodes of congestive failure, a second phonocardiogram was recorded at the apex during a period in which the left ventricle was extremely dilated. The phonocardiogram then revealed the existence of a louder systolic murmur and of a series of diastolic-presystolic vibrations, previously non-existent, which simulated the vibrations usually observed in cases of mitral stenosis (figure 9). Curiously enough, the intensity of the soft diastolic murmur caused by the aortic regurgitation was such that no suspicion of mitral stenosis occurred and no mention of an Austin Flint murmur was made at the time on the basis of clinical auscultation.

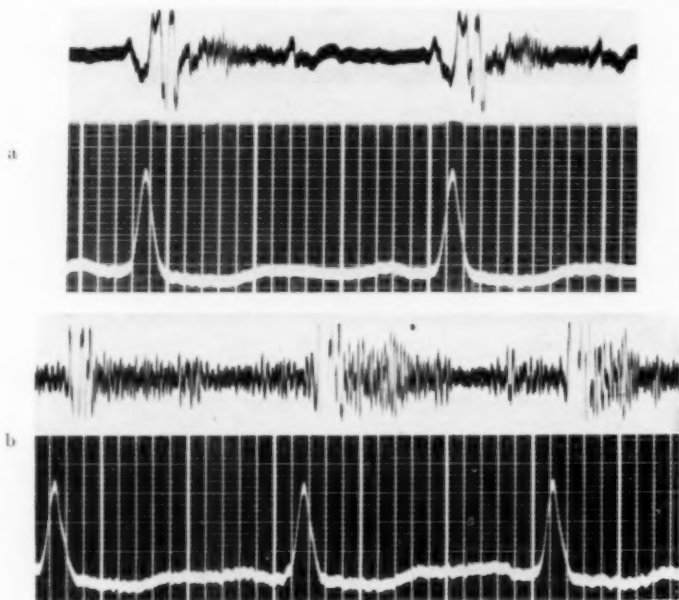


FIG. 9. Phonocardiograms recorded at the apex with a two year interval in a patient with aortic regurgitation and hypertension. In the second tracing, a diastolic-presystolic murmur is present; its appearance coincided with an episode of congestive failure and severe further enlargement of the left ventricle.

The history, the clinical and roentgenological data, and the connection between diastolic vibrations and enlargement of the left ventricle permitted exclusion of mitral stenosis. No follow-up of the case was possible.

Case 11. A patient, age 60, diagnosed as luetic aortitis and aortic insufficiency; myocardial fibrosis with grade 1 a-v block; left ventricular strain. The patient was kept under continuous observation for a period of seven months until death.

A phonocardiogram recorded at the apex showed a very low amplitude of the first and second heart sounds. During diastole, a series of vibrations of large amplitude was visible (figure 10). A comparison of the phonocardiogram with the apex cardiogram revealed that these vibrations coincided with two waves of the cardiogram, one due to the rapid filling and the other to the auricular contraction; the latter was very distant from the beginning of the following ventricular contraction. On the basis of this, a diastolic rumble due to a functional mechanism was admitted (figure 10b). A tracing recorded over the aortic area by means of the logarithmic microphone showed that there was an extremely loud diastolic murmur which coincided

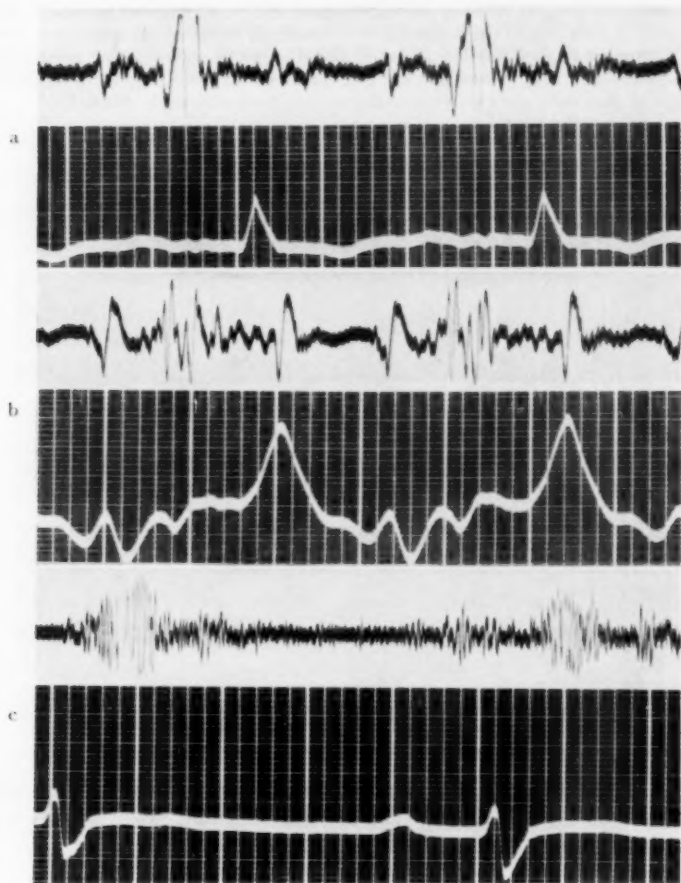


FIG. 10. Phonocardiograms recorded at the apex in a patient with aortic regurgitation, coronary heart disease, and left ventricular strain. In (a) the phonocardiogram is compared with the electrocardiogram; in (b), with the cardiogram. Tracing (c) was recorded a few days later, after an episode of myocardial infarction. A series of mid-diastolic vibrations is present in (a) and (b) while a presystolic murmur is present in (c).

with the apical diastolic murmur mentioned above but which was of a higher pitch and was more prolonged than the other. Subsequent tracings revealed no basic changes in the phonocardiogram but a more and more disordered development of the vibrations. The patient had two episodes of myocardial infarction and died shortly after the second. No postmortem examination was granted.

Case 12. A 52 year old patient entered the Hospital in poor condition with signs of congestive failure. Both the carotid arteries and the jugular veins showed large pulsations; the liver was large and pulsating. Auscultation of the heart revealed a loud, soft, early-diastolic murmur over the aortic area and a diastolic-presystolic rumble over the apex and mid-precordium.

The phonocardiogram showed the existence of an apical diastolic-presystolic murmur (figure 11) and led to the diagnosis of a combined lesion of the aortic and mitral valves. Postmortem examination revealed that the aortic valves were incompetent, that the pulmonary artery was dilated (the pulmonary valve was congenitally abnormal), and that both auriculo-ventricular valves were absolutely normal. The left ventricle was greatly dilated.

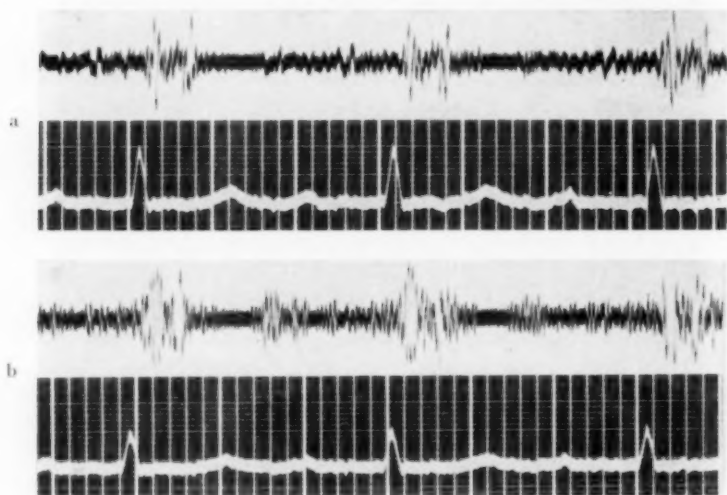


FIG. 11. Tracings recorded in a patient with aortic regurgitation and Austin Flint murmur (postmortem control).

(a) Apical phonocardiogram recorded by means of the stethoscopic microphone.

(b) Apical phonocardiogram recorded by means of the logarithmic microphone.

Tracing (b) reveals a diastolic-presystolic murmur and a systolic murmur.

The final diagnosis was: rheumatic heart disease, aortic insufficiency, possible pulmonic insufficiency. The diastolic murmur, heard and recorded at the apex, therefore, was an *Austin Flint murmur*.

Simulation of Mitral Stenosis by Relative Stenosis of the Mitral Valve without Aortic Regurgitation

Case 13. A 53 year old patient entered the Hospital with a severe picture of congestive failure and uremia. Blood pressure was 220/70 mm. Hg; circulation

time was decreased. The P-R interval was 0.40 sec. The heart was enormous and auscultation revealed the following facts: loud apical and basal systolic murmurs; a questionable, soft, early-diastolic murmur over the base; either one or two sounds at mid-diastole; these sometimes were fused, creating the impression of a diastolic murmur, and sometimes were separated, giving the impression of a four-sound rhythm.

The phonocardiogram (figure 12) confirmed the existence of a mid-diastolic murmur which sometimes was continuous and sometimes split into two phases; one of these immediately followed the P wave of the electrocardiogram. The general interpretation was that the patient was suffering from coronary and hypertensive heart disease, possibly complicated by anemia and/or vitamin-B deficiency. The two diastolic sounds were explained as ventricular and auricular gallop sounds, superimposed on a functional diastolic murmur. The existence of a mild aortic insufficiency was discussed but not admitted.

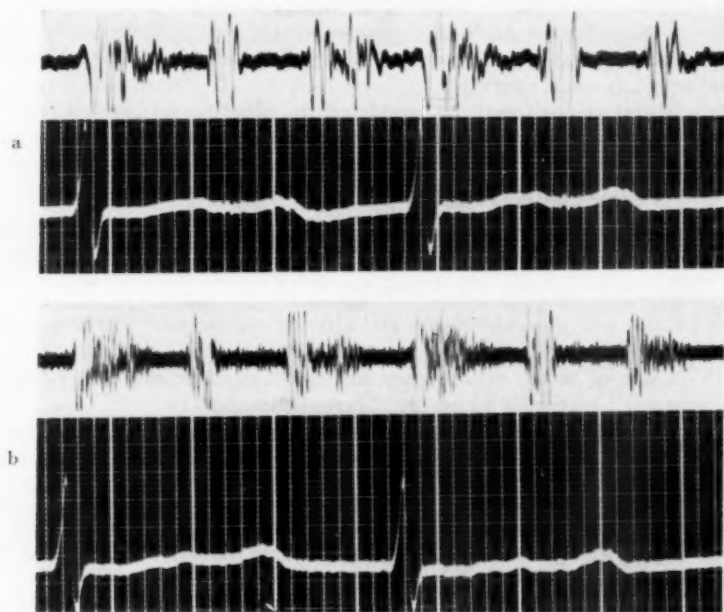


FIG. 12. Coronary and hypertensive heart disease, congestive failure. Both tracings are recorded over the third left interspace. Tracing (a) is recorded by the stethoscopic microphone; tracing (b), by the logarithmic.

There is a diastolic murmur which follows the P wave and is at times split into two phases.

DISCUSSION

The possible existence of a diastolic apical murmur simulating mitral stenosis is known. Occasional phonocardiographic tracings have been taken but no systematic study has been available. Our study was based

on the selection of those cases in which clinical or anatomical proof was obtained that a murmur was functional and on the analysis of the phonocardiographic tracings.

In a series of cases *the phonocardiogram has a decisive value* and permits us to rule out the existence of mitral stenosis. The following types of patients should be included in this group:

(a) *Auricular sound or gallop simulating mitral stenosis.* This possibility is revealed by cases 1 and 2 (figures 1 and 2) and is more common whenever the heart rate is irregular. This group should include those cases of mitral insufficiency having either auricular or ventricular gallop (cases 6 and 7; figure 6), and those cases of aortic insufficiency having an auricular gallop (case 9; figure 8) in which an erroneous diagnosis of Austin Flint murmur was made.

(b) *Bundle branch block and fibrosis of the mitral valve simulating mitral disease* through the existence of a systolic murmur and a loudly split second sound (case 3; figure 3).

(c) Mitral stenosis may be simulated by *adhesive pericarditis*, either through a late systolic snap giving a reduplication of the second sound (case 4; figure 4) or through an early-diastolic snap connected with the dynamics of the constricted heart (case 5; figure 5).

In a second series of cases, *the phonocardiogram has no decisive value* because the tracings reveal vibrations which simulate those of mitral stenosis. This group includes the following:

(a) Cases with *auricular flutter* and a functional diastolic murmur at the apex (case 8; figure 7).

(b) Cases of *aortic insufficiency and apical diastolic murmur (Austin Flint murmur)* (cases 10, 11 and 12, figures 9, 10 and 11).

(c) Cases of *coronary and hypertensive heart disease* with a functional diastolic rumble of the apex but no aortic regurgitation (case 13, figure 12).

In the first group of cases the interpretation is simple because the diagnosis is based on an *auscultatory illusion* due to a crescendo-type of the first sound, an auricular or ventricular gallop, a split second sound caused by bundle branch block, or a systolic snap from the traction of adhesions.*

In the second group of cases, on the other hand, the *actual existence of a diastolic rumbling murmur is proved by the phonocardiogram*. If there is aortic insufficiency, the murmur should be called an Austin Flint murmur. If there is no aortic insufficiency, no special name is given to these murmurs. The simple grouping of these cases indicates that the mechanism of production of the murmur is similar. It is likely that the recorded vibrations are due to the rapid passage of blood from a large left auricle through a normal mitral orifice into a tremendously enlarged left ventricle. In conclusion,

* During the publication of this study, eight cases of auditory illusion due to a crescendo-type of the first sound have been presented by Alimurung, Rappaport and Sprague.¹⁷

we think that the explanation given by P. D. White should be accepted in preference to older explanations. It is likely that such a murmur is encountered seldom because its production requires the coexistence of two factors: An increased speed of circulation and a disproportion between a normal mitral orifice and the large chambers of the left heart, especially a large left ventricle (relative stenosis of the mitral valve).

SUMMARY

A clinical and graphic study of apical diastolic murmurs simulating those of mitral stenosis is reported. The study includes cases of mitral insufficiency without appreciable stenosis, aortic insufficiency (Austin Flint murmur), coronary and hypertensive heart disease, adhesive pericarditis, and disturbances of the rate and rhythm.

In a first group of cases, the phonocardiogram revealed that the murmur was not caused by mitral stenosis. This group included cases with arrhythmia, mitral insufficiency, adhesive pericarditis, and some cases of coronary and hypertensive heart disease. In most of these cases, the so-called murmur resulted from an auscultatory illusion and was caused either by a gallop or by a crescendo-type of the first sound.

In a second group of cases, the phonocardiogram revealed diastolic-presystolic vibrations simulating those of mitral stenosis; the functional nature of the murmur was revealed by either the subsequent clinical course or negative postmortem findings. This group included patients with aortic insufficiency (Austin Flint murmur), coronary heart disease, and auricular flutter.

It is concluded that, while the phonocardiogram permits recognition of the nature of the murmur in a large number of cases, it fails to do so in a minority.

The cause of the functional diastolic murmur at the apex is discussed.

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THERAPY OF ACUTE BARBITURATE POISONING: REPORT OF THREE CASES *

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THE following cases are believed to be of interest because: (1) They illustrate recovery from barbiturate intoxication, potentially fatal in degree, without the use of picrotoxin. (2) Correlation between the clinical status and blood barbiturate levels was made.†

CASE REPORTS

Case 1. (Figure 1.) This 40 year old taxi driver was perfectly well the evening before admission. At 8 a.m. on the day of admission, the patient's wife noticed that her husband was "asleep and breathing very heavily." At noon, the first attempt at awakening was made, without success. The local physician was called; he administered adrenalin and caffeine with sodium benzoate. The patient was admitted to the hospital at 2:45 p.m. on August 14, 1947.

Physical Examination on admission: Temperature (rectal) 100.6° F.; pulse, 90; respirations, 24; blood pressure, 84/64 mm. Hg; weight (taken later) 73 kg. The patient was lying flat in bed, completely unresponsive. Respirations were deep, regular, almost entirely diaphragmatic. The pulse was full and regular. The pupils were small and reacted to light minimally. The corneal reflexes were absent. The fundi were normal. The neck was supple. The lungs, heart, abdomen, genitalia, rectum and extremities were normal. There was a slight right ankle jerk; no other deep, superficial, or pathological reflexes were elicitable.

Laboratory Data: The blood Hinton test was negative. The urine was negative except for a 1+ albumin. The hemoglobin was 13.7 gm., the hematocrit 44, with a normal sedimentation rate (Wintrobe), and the white blood cell count was 13,900 with a slight shift to the left. The carbon dioxide combining power was 23.6 millimols per liter. The blood bromide was 0. The blood urea nitrogen, blood sugar, and total plasma proteins were normal. Lumbar puncture showed an initial pressure of 95 mm. of water with a normal cell count, chloride, sugar and protein content and a negative Hinton test. Roentgenograms of the heart, lungs and skull were normal.

Hospital Course: First day: Gastric aspiration was carried out upon admission with recovery of only a small amount of gastric contents. The patient received 1,000 c.c. of 5 per cent dextrose in saline intravenously. Intramuscular penicillin was started in doses of 30,000 units every four hours. The patient was turned and his pharynx suctioned every half hour. By evening, his tendon reflexes had returned

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† The authors are indebted to Dr. R. S. Fisher, Department of Legal Medicine, Harvard Medical School, for his generous coöperation in performing the barbiturate determinations in these cases and for allowing the use of his data in this report. These determinations were made with a new rapid and accurate spectrophotometric technic.^{1, 2}

except for the biceps bilaterally. His blood pressure rose to 120/80. He remained deeply comatose.

Second day: The initial blood barbiturate level at 10:30 a.m. was 20.6 mg. per cent and thereafter steadily fell (figure 1). The patient's reflexes in the morning were slightly hyperactive with bilateral sustained clonus. A second lumbar puncture was normal. He began hyperventilating (rate 40 to 44), but the carbon dioxide combining power went up to 35 millimols per liter. The patient was bronchoscoped late in the afternoon and his respirations returned to normal. His hyperreflexia stopped. His rectal temperature rose to 104° F. and he remained deeply comatose. He received intravenously 2,000 c.c. of 10 per cent dextrose in water.

Third day: At 8 a.m. the patient's blood barbiturate level was 16.4 mg. per cent. His deep tendon reflexes were again hypoactive and he remained deeply comatose. The blood chloride was 107 mEq/l and the carbon dioxide combining power 23.6

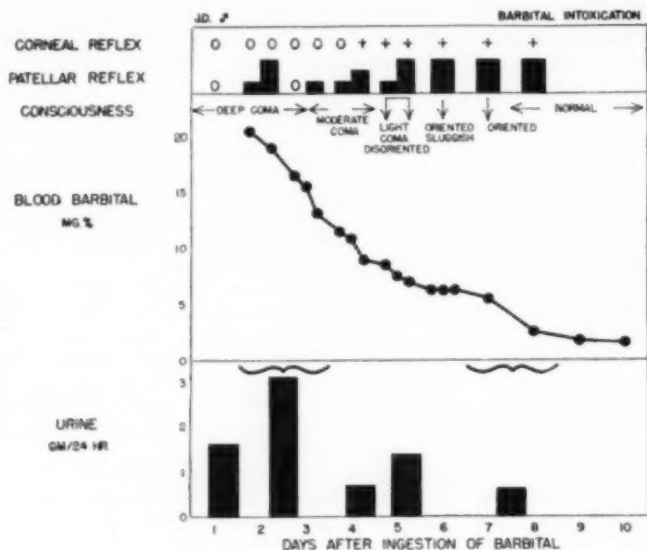


FIG. 1.

mM/l. The patient received 105 gm. of sodium succinate (15 gm. initial dose and 30 gm. every three hours for three additional doses) in 5 per cent dextrose in water. Late in the evening his reflexes became more active, the gag reflexes returned, and he began moving his head. The rectal temperature fell to 102° F.

Fourth day: At 8 a.m. the blood barbiturate level was 11.8 mg. per cent. The patient began to show some response to painful stimuli, but remained semi-comatose. Tube feeding was initiated.

Fifth day: At 8 a.m. the blood barbiturate level was 8.5 mg. per cent. During the morning the patient's corneal reflexes became elicitable and he gradually began moving his arms and legs spontaneously and opened his eyes. By 5:00 p.m. he was able to give monosyllabic answers to questions. The blood barbiturate level at 8:00 p.m. was 7.1 mg. per cent. Hyperreflexia and ankle clonus were present bilaterally and the patient was incontinent of urine.

Sixth day: At 8 a.m. the blood barbiturate level was 6.3 mg. per cent. At that time, the patient became quite lucid and was continent. Oral feedings were begun. Thereafter, the patient improved steadily. Ankle clonus remained until discharge. By the eighth hospital day, he was afebrile. The final blood barbiturate level on the tenth day was 1.7 mg. per cent. He showed no clinical evidence of brain damage and was discharged on the fifteenth hospital day. Although 7.4 gm. of barbital were recovered and identified from his urine, the patient never admitted having ingested the drug.

Case 2. (Figure 2.) This 47 year old unmarried woman took 20 to 24 capsules (2.0 to 2.4 gm.) of pentobarbital sodium ("Nembutal") approximately 14 hours before admission. She had had supper six hours prior to the ingestion of the drug. The following morning, March 29, 1948, she could not be aroused and was brought to the hospital.

Physical Examination on admission: Temperature (rectal) 94.6° F.; pulse 60; respirations 24. Systolic blood pressure 76, diastolic pressure unobtainable. Weight

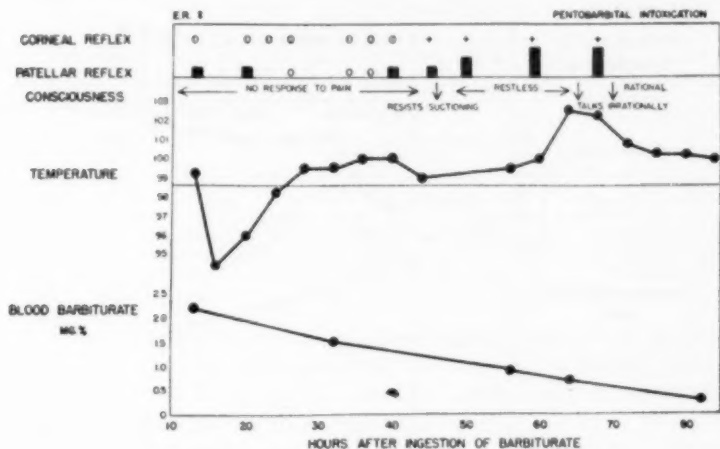


FIG. 2.

(taken later) 52 kg. The patient was a thin, deeply comatose woman. Her skin was cold and dry. Her pupils were constricted and responded sluggishly to light. The ocular fundi were normal and the neck, lungs, heart, and abdomen were negative. There was no response to painful stimuli. The knee jerks were hypoactive. The corneal reflexes were absent. There was no response to plantar stimulation.

Laboratory Data: The blood barbiturate level on admission was 2.2 mg. per cent. The blood Hinton test was negative. The urine was negative except for a 1+ protein. The hemoglobin was 13.6 gm. and the hematocrit 38 with sedimentation rate of 42 mm. per hour (Wintrobe). The white blood cell count was 6,000. The blood urea nitrogen, blood sugar, total protein, blood chloride, all were normal. The brom-sulfalein excretion test was normal. Phenolsulfonphthalein excretion in 30 minutes was 35 per cent, in two hours 55 per cent. The last two tests were carried out after the patient had recovered from coma. An electrocardiogram was normal.

Hospital Course: On admission the patient was given 1.0 gm. of coramine intravenously and 0.5 gm. of caffeine with sodium benzoate intramuscularly. Shortly

after admission, the blood pressure became unobtainable. After infusion of 250 c.c. of plasma, the blood pressure rose to 100/50. The head of the bed was subsequently elevated slightly, the patient was turned every hour, oxygen was administered by mask and constant urinary catheterization was instituted. Caffeine with sodium benzoate, 0.5 gm. every four hours and penicillin, 100,000 units every six hours, were given intramuscularly. On the third day, the temperature rose to 102.4° F. A roentgenogram of the chest showed a small irregular density near the right hilar region. Blood and urine cultures were sterile and throat cultures showed a normal flora. Three days later, the x-ray abnormality had completely cleared and the temperature had returned to normal. In figure 2, changes in the patient's temperature, state of consciousness, corneal and patellar reflexes are correlated with the blood barbiturate levels at successive points in her course.

Case 3. (Figure 3.) This 59 year old white divorced woman had been treated for one year for "mental depression." Approximately 11 hours before admission,

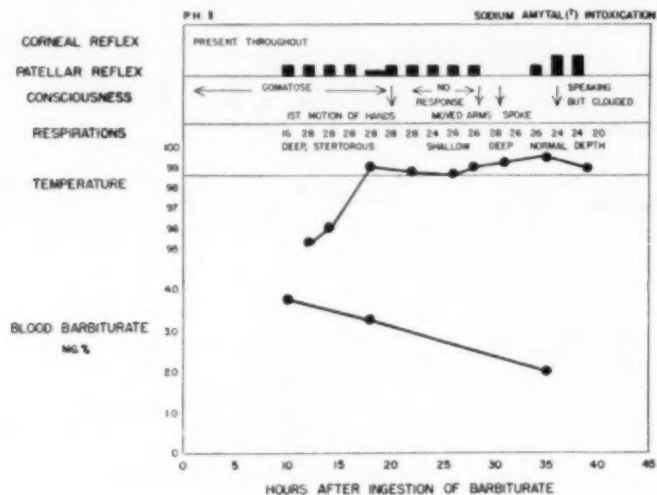


FIG. 3.

she swallowed 17 to 18 capsules of sodium amytal, 0.2 gm. each (total 3.4 to 3.6 gm.). One hour before admission on April 1, 1948, the patient was found comatose.

Physical Examination on admission: Temperature (rectal) 95.4° F.; pulse 80; respirations 16; blood pressure 94/70. Weight (taken later) 50 kg. The patient was a deeply comatose, well developed, thin woman, breathing stertorously. Her skin was clear, with good hydration. Her pupils were constricted and reacted sluggishly to light. The ocular fundi, neck, heart, lungs and abdomen were negative. A neurological examination showed deep coma, with lack of response to painful stimuli, depressed gag reflex and hypoactive equal tendon reflexes.

Laboratory Data: The blood barbiturate level was 3.6 mg. per cent. The blood Hinton test was negative. Urine examinations were negative. The hemoglobin was 16.7 gm., with a hematocrit of 48. The sedimentation rate was 8 mm. per hour (Wintrobe) and white blood count was 6,200. The blood urea nitrogen, blood sugar, total plasma proteins, carbon dioxide combining power, blood chloride, thymol tur-

idity, serum bilirubin, prothrombin time were normal. Bromsulfalein excretion test was normal. Phenolsulfonphthalein excretion was 40 per cent in 30 minutes, 55 per cent in two hours. The last two tests were carried out after the patient had recovered from coma. A stool specimen was guaiac negative. An electrocardiogram was within normal limits.

Hospital Course: On admission gastric lavage was unsuccessful. The patient was given oxygen by mask, constant urinary drainage, intramuscular penicillin, 100,000 units every six hours, and caffeine with sodium benzoate, 0.5 gm. every two hours. She was turned every half hour and her pharynx was suctioned frequently. On the first day, the patient was given 250 c.c. of plasma intravenously followed by 1,000 c.c. of 5 per cent dextrose in saline and 1,000 c.c. of 5 per cent dextrose in water. On the second day, 1,000 c.c. of 5 per cent dextrose in saline and 1,000 c.c. of 5 per cent dextrose in water were given intravenously. By the third day, she was able to take adequate fluids by mouth. In figure 3 the changes in the patient's temperature, respiration, patellar reflex, and state of consciousness are correlated with the blood barbiturate levels at successive points in her course.

COMMENT AND DISCUSSION

The barbiturate dosage taken by each of our patients and the potentially fatal dose of each barbiturate are given in table 1.

TABLE I

Case	Drug	Dose Ingested	Potentially Fatal Dose
1	Barbital	More than 10 gm.	6.0 gm. (3)
2	Pentobarbital	2.0-2.4 gm.	1.5-3.0 gm. (4)
3	Amytal	3.4-3.6 gm.	2.0-3.0 gm. (5)

In Case 1, ingestion of barbital was not admitted, but 7.4 gm. of barbital were recovered from the urine and it is estimated from the blood levels that at least 10 gm. must have been ingested. In Cases 2 and 3, the quantities of pentobarbital sodium and sodium amytal taken were known definitely. In all three cases, most clearly in Case 1, potentially fatal doses of barbiturates were ingested.

In Case 2, the patient awakened when the blood concentration of pentobarbital had fallen to approximately 1.0 mg. per cent. This figure corresponds closely with those in other cases of pentobarbital poisoning in which the blood levels were obtained, as tabulated by Fisher.² Cases with barbital and amytal intoxication similarly studied are not available for comparison.

Patients with barbiturate intoxication are often first regarded by their relatives as in normal sleep and are usually not hospitalized until 10 to 14 hours after ingestion of the drug. In contrast to persons with extremely massive barbiturate poisoning who die before hospitalization, hospital cases are a somewhat selected group, relatively milder, and frequently on their way to recovery. We believe that for such patients the main causes of death, probably in order of importance, are (1) pulmonary complications; (2) circulatory stasis; (3) cerebral edema; and (4) respiratory failure due

to the direct depressant effect of the drug on the respiratory center. Therapy is directed at preventing or controlling these dangers without superimposing avoidable difficulties.

1. The serious early pulmonary complications are atelectasis and pulmonary edema; later complications include bronchopneumonia and lung abscess. Careful clinical observations with skillful and constant nursing are of foremost importance in the prevention of these difficulties. Frequent turning of the patient does much to prevent atelectasis and hypostatic pneumonia. If shock is not imminent or present, maintenance of adequate respiratory rate and volume is favored by slight elevation of the head of the bed. Frequent suctioning deep in the pharynx serves both to remove mucus and to stimulate deeper inspiration. Bronchoscopy may even be desirable, as in Case 1, to remove mucous plugs. Atropine is best avoided, except in small doses when there is excessive secretion, because of its tendency to inspissate mucous plugs, preventing their dislodgement. Diminished oxygenation due to decreased ventilation can be improved by oxygen without positive pressure. Pulmonary edema should be promptly treated with oxygen, possibly under positive pressure, and aminophyllin, digitalization, tourniquets and venesection, if no contraindication to any of these measures exists. Finally the antibacterial drugs should now be used in every comatose case of barbiturate intoxication to minimize the danger of secondary pulmonary infection.⁶

2. The patient with circulatory stasis should be covered with warm blankets, put in a slight Trendelenburg position and given plasma or blood and intravenous fluids. When the blood pressure is low, neosynephrin, which elevates and maintains the blood pressure without tachycardia,⁷ may well be the supplementary drug of choice. The usual dose is about five times that of epinephrine.

3. Cerebral edema is difficult to evaluate clinically, although it is frequently found at autopsy. Prolonged anoxia, which may give rise to such cerebral edema, can be allayed with oxygen; 50 per cent dextrose in water, salt-free albumin, and lumbar puncture have been advocated also.

4. Death due to direct central nervous system depression by the barbiturates is probably uncommon, at least in hospital cases.⁸ Rapid elimination of the drug is, of course, essential. Gastric lavage, preferably with sodium phosphate left in the stomach, should be used in all cases seen within a few hours after ingestion of the drug. Constant suction on the tube as it is withdrawn is necessary to avoid aspiration of the fluid. Intravenous fluids, sufficient to produce a urinary output of 1,500 to 2,000 c.c. daily, are indicated to promote excretion of the drug. Care should be taken, however, in the anuric cases, not to "push" the fluids, but rather to be guided by the state of hydration and by frequent determinations of the serum electrolytes. Care is necessary during the infusion of saline to avoid precipitating cerebral and pulmonary edema. In comatose patients with bladder atony, constant urinary drainage is an adjunct of obvious importance.

Central respiratory depression can be combated, without convulsant dangers, with a drug such as caffeine in doses of 0.5 gm. every two to four hours. If the depression is very severe, a respirator may be of valuable assistance.⁹ In all of our cases, a Drinker respirator was readily available for prompt treatment of sudden respiratory failure.

The first patient was treated with sodium succinate, 105 gm. being given intravenously over a period of 12 hours. This form of treatment was first used by Soskin and Taubenhaus,¹⁰ based on the original work *in vitro* by Quastel and Wheatley.¹¹ In this single case, no definite impression can be given as to its rôle in barbiturate therapy.

Finally, reference in some detail should be made to the use of picrotoxin, since this drug has been widely used, at least in this country, in the treatment of barbiturate intoxication. There has been controversy over the indications for its administration and over its possible effect on the clinical course and outcome in cases of varying severity.

That animals may survive as much as three times the lethal dose of a barbiturate when treated with picrotoxin seems clear from the original laboratory experiments of Tatum and co-workers.^{12, 13, 14} On the other hand, the rôle of picrotoxin in the therapy of human intoxication is not so well defined. While many severe cases of poisoning have been reported with recovery following the use of picrotoxin, many other similarly severe cases have recovered satisfactorily with supportive therapy alone.^{15, 16} The overall mortality rate in the series of 643 cases reported by Hambourger which were not treated with picrotoxin was 7.3 per cent.³ On the other hand in the series of 130 cases treated with picrotoxin which we have been able to collect from the literature,^{8, 9, 17 to 49} there were 24 deaths (18.5 per cent). The difference is interesting, even though the two series are hardly comparable since a great number of the picrotoxin treated cases were severe.

Any discrepancy between the animal and human results, aside from species differences, may well be explained in part by the fact that the humans who are not given picrotoxin are nonetheless given the benefit of therapy as discussed above. An experiment comparing the survival rate of animals given full supportive therapy with and without picrotoxin would be more significant.

Indeed, we believe that picrotoxin may at times be harmful. We refer particularly to the occurrence of convulsions. Among the cases reported which were treated with picrotoxin (excluding those with inadequate histories, those with doses of picrotoxin which were insignificant or not stated or with other convulsant drugs used in sufficient quantities) convulsions ascribable to picrotoxin occurred in 20.3 per cent (13 of 64 cases).

In summary of the status of picrotoxin, the published data appear to contain no statistical evidence to support the contention that picrotoxin has reduced the overall mortality in barbiturate intoxication, or that in the ordinary case of deep narcosis it lessens the chances of fatality. Use of this drug should probably be considered only in selected cases doing badly

despite full supportive therapy; its administration should be reserved for physicians skilled in the best methods and familiar with the hazards of this drug.

SUMMARY

Three cases of potentially fatal barbiturate intoxication due to barbitol, sodium pentobarbital and sodium amytal, respectively, are presented. All three patients recovered under a supportive regime of therapy, without the use of picrotoxin. Blood barbiturate levels determined with a new spectrophotometric technic, were correlated with the clinical status. Supportive therapy is outlined in some detail and the use of picrotoxin is discussed.

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PULMONARY INVOLVEMENT IN TYPHOID AND PARATYPHOID FEVERS *

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CLINICAL evidence of pulmonary involvement in typhoid and the paratyphoid fevers is well recognized by most textbooks of medicine and the rather common occurrence of signs and symptoms of bronchial irritation which is usually referred to as bronchitis, as well as the possibility of complication by actual pneumonia are pointed out. The pathogenesis of many of the major clinical manifestations in typhoid and paratyphoid fevers has been explained reasonably well on the basis of studies both in man and in experimental animals.¹ However, the reasons for the pulmonary involvement which may occur are poorly understood.

Earlier medical writings display a greater appreciation of the frequency with which pulmonary signs occur in the enteric fevers, whereas most modern textbooks merely mention that cough and bronchitis may be seen as early symptoms, and acknowledge the possibility of later pulmonary complications. For example, in an old English textbook of medicine² it is stated, "bronchitis of some degree is a constant feature of enteric fever, characterized by short cough, little or no expectoration, and by harsh breathing, with abundant or at times scanty rhonchi." Typhoid fever with sudden onset and a clinical picture, in which pulmonary signs and symptoms predominated, received early attention in the European medical literature as pneumo-typhoid. During the years 1900 to 1909 bronchopneumonia was reported as a complication of typhoid fever in from 0.5 to 2.5 per cent of the cases at London Fever Hospitals, but the figure of 11 per cent was cited by other sources at this time.³ Pneumonia was said to occur in from 1.5 to 3.5 per cent of typhoid cases. French authors of the same period, e.g. Nobecourt and Peyre,⁴ claimed that pulmonary complications occurred in about 10 per cent of paratyphoid A fevers, and in 4 per cent of paratyphoid B infections. In a recent analysis of 360 cases of typhoid fever,⁵ respiratory signs and symptoms were reported in 60 to 80 per cent of the cases, and 12 per cent had actual pneumonia. However, no further details were given in this paper as to incidence and variety of physical findings in the chest; it was

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considered that râles, except in the presence of pneumonia, represented hypostatic pulmonary congestion.

This paper reports observations and studies made between January 1948 and March 1949 on cases of typhoid and paratyphoid fevers in Egypt. The report includes (1) tabulation of incidence and degrees of pulmonary involvement; (2) types of physical signs encountered; (3) bacteriological findings on sputum and on bronchial secretions aspirated under direct vision; and (4) three case summaries of representative patients. Studies of the cytology of bronchial secretions have also been done.⁶

Selection of Cases: The cases which comprise this present study were patients admitted to the study ward of the United States Naval Medical Research Unit No. 3, located at the Abbassia Fever Hospital in Cairo, Egypt. All patients were males between the ages of 9 and 35 years, the great majority between 15 to 25 years old, obtained from the third class (low-income group) general public wards of the Fever Hospital. There was no attempt at selection of cases because of the presence or absence of pulmonary findings. The patients were the object of other studies as well. Cases were selected indiscriminantly on the basis of positive blood culture taken on new male admissions to the Fever Hospital who were regarded as possible cases of enteric fever. Save for one patient who was found to have miliary tuberculosis also on admission, and one patient with probable bronchiectasis who will be discussed in greater detail later, no other major diseases were concurrent in the group studied. While infestation with bilharzia and intestinal parasites was common in these patients, major clinical manifestations of these diseases which might have influenced the studies here reported were not apparent. The diagnosis of all cases included in the study was proved bacteriologically. Organisms isolated were identified on the basis of motility, biochemical reaction, and slide agglutination with specific "O" antisera obtained from the Standards Laboratory, Oxford, England. In addition, many of the strains were sent to the Enteric Pathogen Laboratory in charge of Commander L. A. Barnes, MSC, USN, at the Naval Medical Research Institute, Bethesda, Maryland, for verification. The patients were under the care of naval medical officers. Analysis of pulmonary findings in our patients was not contemplated initially; hence, it is felt that special note was not made unconsciously of minimal findings, nor were existing signs exaggerated, in the interest of this study.

PULMONARY FINDINGS IN 80 CASES OF TYPHOID AND PARATYPHOID FEVERS

The breakdown of the total group into specific diseases is as follows:

Typhoid fever	49 cases
Paratyphoid A	28 cases
Paratyphoid B	1 case
Paratyphoid C	2 cases
Total	80 cases

There was considerable variation in the clinical course of each individual case. Some were seen relatively late in the disease, a few were febrile only a few days, but the majority of the cases were first seen during the second week of illness and exhibited characteristic clinical courses. There was a total mortality of four cases. Two typhoid patients died with pneumonia as a complicating cause of death, and two typhoid patients died of a perforated bowel with peritonitis. A third perforation occurred, but operation saved the patient after a long and stormy course.

Degrees of Pulmonary Involvement: The entire series of patients, both typhoid and paratyphoid, was subdivided into four groups according to the degree of pulmonary involvement exhibited on the basis of physical signs. The results are shown in table 1. The classification was derived from the records of physical examination upon admission to our ward and subsequent progress notes. Such a division was necessarily arbitrary, but in the great majority of cases no difficulty was encountered in assigning a particular case to its classification. The criteria for those cases showing no pulmonary signs is self-evident; however, it should be noted that since all cases were not necessarily examined at frequent intervals, some of them may have shown temporary findings of some degree during their hospital stay which were missed (Group 1). Patients who had such signs as scattered râles, rhonchi, wheezes, and other minor changes in breath sounds, either alone or in combination, on admission or during a few days of their illness were placed in the group showing minimal signs (Group 2). The cases designated by moderate signs were those who showed essentially the same type of physical signs as those in the "minimal" group, but to a greater degree on entry, or over a longer time than on a single examination (Group 3).

The last group, those showing prominent signs, exhibited persistence of their findings over four or five days to a week or even longer. Persistent loud, harsh breath sounds, various types of musical rhonchi and râles, similar to those heard in asthmatics were frequently encountered (Group 4).

The two patients in the miscellaneous group were special cases that did not strictly fit elsewhere. One was a patient with repeated positive blood cultures for typhoid, who also had miliary tuberculosis by x-ray, and early tuberculous meningitis. The other case was that of a 23 year old Egyptian soldier who entered the ward on what he claimed was the seventh day of a febrile illness. An initial blood culture was positive for Para A, but the patient presented with classic signs of pneumonia and a pneumococcus type I was cultured from the sputum. The fever subsided promptly on penicillin therapy. The absence of either somatic or flagellar agglutinins in serial blood specimens leaves a specific diagnosis in even further doubt.

The overall incidence of pulmonary signs in this series of 80 patients is 64 per cent. Even if only those patients in whom physical signs of moderate

TABLE I
Degrees of Pulmonary Involvement in 80 Cases of Typhoid and Paratyphoid Fever

Group 1 Cases showing no physical signs of pulmonary involvement	Group 2 Cases showing minimal signs of pulmonary involvement	Group 3 Cases showing moderate signs of pulmonary involvement	Group 4 Cases showing prominent signs of pulmonary involvement	Miscellaneous (not classified)
X (typhoid)	X (typhoid)	X (typhoid)*	X (typhoid)	X (typhoid)
X (typhoid)	X (typhoid)	X (typhoid)*	X (typhoid)*	X (Para A)
X (typhoid)	X (typhoid)	X (typhoid)	X (typhoid)*	
X (typhoid)	X (typhoid)	X (typhoid)	X (typhoid)	Total 2 cases
X (typhoid)	X (typhoid)*	X (typhoid)	X (typhoid)	
X (typhoid)	X (typhoid)	X (typhoid)	X (typhoid)	1 typhoid
X (typhoid)	X (typhoid)	X (typhoid)	X (typhoid)	1 Para A
X (typhoid)	X (typhoid)	X (typhoid)	X (typhoid)	
X (typhoid)	X (typhoid)	X (Para A)*	X (typhoid)	
X (typhoid)	X (typhoid)	X (Para A)	X (typhoid)*	
X (typhoid)	X (typhoid)	X (Para A)	X (typhoid)	
X (typhoid)	X (Para A)	X (Para B)	X (typhoid)	
X (typhoid)	X (Para A)		X (Para A)	
X (typhoid)	X (Para A)	Total 12 cases	X (Para A)	
X (typhoid)	X (Para A)		X (Para A)	
X (typhoid)	X (Para A)	8 typhoid	X (Para A)	
X (typhoid)	X (Para A)	3 Para A	X (Para A)	
X (typhoid)	X (Para A)	1 Para B	X (Para A)	
X (Para A)			X (Para A)	
X (Para A)	Total 17 cases		X (Para A)	
X (Para A)			X (Para A)*	
X (Para A)	11 typhoid		X (Para A)	
X (Para A)	6 Para A		X (Para C)*	
X (Para A)			Total 22 cases	
X (Para A)			12 typhoid	
X (Para A)			9 Para A	
X (Para C)			1 Para C	
Total 27 cases				
17 typhoid				
9 Para A				
1 Para C				

* Cases complicated by pneumonia.

17 of the 49 typhoid cases showed no physical signs.

9 of the 28 Para A cases showed no physical signs.

11 of the 49 typhoid cases showed minimal signs.

6 of the 28 Para A cases showed minimal signs.

8 of the 49 typhoid cases showed moderate signs.

3 of the 28 Para A cases showed moderate signs.

12 of the 49 typhoid cases showed prominent signs.

9 of the 28 Para A cases showed prominent signs.

and prominent degree are considered as showing significant evidence of pulmonary involvement (Group 3 and 4), the incidence is 42 per cent.

Types of Physical Signs Encountered: In those cases exhibiting only minimal signs (Group 1) the most common findings were rhonchi, decreased breath sounds, and squeaks, in that order. In Groups 3 and 4 the most common findings were râles and rhonchi. Next in frequency were decreased breath sounds, squeaky breath sounds, dullness to percussion, and wheezes. Varieties and frequency of incidence of each are listed below:

PHYSICAL FINDINGS IN 34 CASES OF TYPHOID AND PARATYPHOID FEVERS
WITH MODERATE OR PROMINENT PULMONARY SIGNS

Râles	71%	Harsh breath sounds	15%
Rhonchi	68%	Whistles	12%
Decreased breath sounds	44%	Groans	9%
Squeaks	44%	Bronchial breathing	9%
Dullness	35%	Friction rub	3%
Wheezes	32%		

(The frequency of the above signs is listed on a patient basis only. Their duration was not used in arriving at the above percentages, e.g., râles were noted at one time or another in 24 of the 34 cases.)

Râles, when heard, were usually moist and fine, whereas harsh and loud rhonchi were the rule. Neither râles nor rhonchi were restricted to any particular phase of respiration. Decreased breath sounds tended to be patchy in location, and dullness was confined almost always to the lower lung fields. The most striking findings, when they occurred, were harsh breath sounds, high pitched wheezes, squeaks, and whistles. These were often identical with the type of breath sound occurring with bronchial asthma. Single types of physical findings were rare, combinations were the rule.

The findings noted above conform very well to accepted descriptions of physical signs produced by changes in both large and small pulmonary air passages.⁷ They confirm the impression that whatever pulmonary signs do occur with any regularity in association with the enteric fevers are due primarily to involvement of the bronchi.

Cases Complicated by Pneumonia: Nine of the total of 80 cases were complicated by pneumonia, or an incidence of 11 per cent. Pneumonia occurred in six typhoid cases, two cases of paratyphoid A, and one case of paratyphoid C. The involvement was considered to be bronchopneumonia in all except two cases of typhoid who each showed at autopsy gross consolidation of more than half of two separate lobes of the lungs. Diagnosis of pneumonia was based upon clinical grounds alone in one case (typhoid), on autopsy in three cases (all typhoid), and on x-ray changes plus clinical findings in five cases (one para A, one para C and three typhoids). Location of the involvement was in both upper lobes in one case (typhoid), diffusely throughout the lungs in one case (typhoid), in both upper and lower lobes in one case (para C), and in the lower lobes in the remaining six cases (two para A and four typhoids). Pleural effusion occurred in association with the pneumonia in two cases (one para A and one typhoid), but in both cases the fluid was aspirated and cultured after the patient had been on chemotherapy for at least 24 hours, and the fluid was found to be sterile.

Two of the paratyphoid A patients who were complicated by pneumonia were interesting in that the pneumonia developed late in the disease. In one, signs appeared on the fourteenth day of illness, after the temperature had shown a progressive decline toward normal. In the other case, the evidence of pneumonia appeared on the twenty-fifth day of disease, after the fever had subsided and the temperature had been normal for one day.

Bacteriologic Findings Associated with Pulmonary Involvement: Unfortunately bacteriological studies of sputum or bronchial secretions were not made in all of the 80 cases. However, 19 consecutive cases were investigated by serial cultures of sputum or bronchial secretions obtained by direct aspiration. Twelve of these had repeated aspiration done two or three times during the acute stage of their disease and again in convalescence. In the remaining seven cases sputum was cultured at least three times during the acute stage of disease. Of the 19 patients studied in this manner, all but three belonged to groups 2, 3, and 4 in regard to degree of pulmonary signs they exhibited. Particular attention was paid to the possibility of recovering typhoid or paratyphoid organisms. In only one of the cases studied was the etiological agent of the disease recovered from sputum or bronchial secretions; this was a case of typhoid fever who died of a perforated bowel four days after *S. typhi* was isolated from aspirated bronchial secretions. The organisms, mixed with a fair number of coliform bacteria, grew out on direct plating of aspirated material to a plate of MacConkey's agar.

Pneumococci were isolated in four of the 19 cases. One of these patients, para A on initial blood culture, with a type I pneumococcal lobar pneumonia responding promptly to penicillin, has been already discussed. A second case of typhoid fever showed type XIX pneumococci on eight serial sputum cultures, but did not have pneumonia. This case undoubtedly represented a carrier. In two of the cases with pneumonia, type I and II pneumococci respectively were isolated. One of these two cases will be presented in greater detail later.

Cough and Character of Sputum: Accurate observations regarding cough and the production of sputum were made only in a consecutive series of 16 cases. The only conclusions which can be drawn from this small group and from the remainder of the cases seen was that non-productive cough was a frequent finding, both in the history of illness before hospitalization and while observed in the hospital. When sputum was produced it was usually scanty and not characteristic. In only one case (typhoid), in whom bilateral lobar pneumonia was found at autopsy, was bloody sputum noted.

CASE REPORTS

The clinical summaries of three patients who illustrate particular features of the problem of pulmonary involvement in the enteric fevers are given below:

CLINICAL SUMMARY FOR CASE 1

History and Physical Examination: A 17 year old Egyptian laborer entered the hospital with an 11 day history of chills, headache, fever, diarrhea, and vomiting. The vomiting ceased after the third day, but the diarrhea persisted for the first five days, and the chills, fever and headache continued. No significant past medical history. Physical examination on entry showed: Blood pressure 96/58 mm. Hg, pulse 100, respiration 36. Rectal temp. 103.8° F. The patient was poorly developed and nourished (weight 77 pounds), acutely and severely ill, but oriented. Skin hot, dry

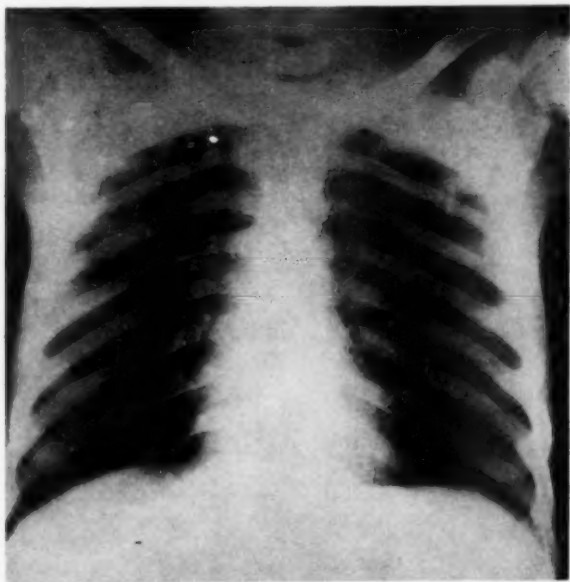


FIG. 1. *Case 1.* Admission film, twelfth day of disease. Chest relatively clear.

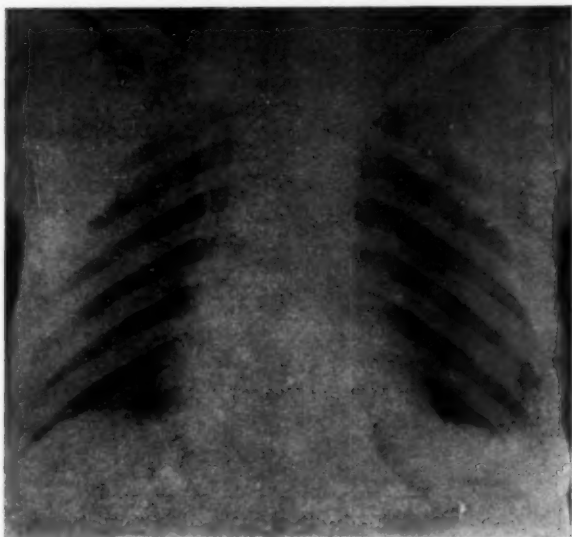


FIG. 2. *Case 1.* Twenty-fourth day of disease. Poor film due to rotation, but cardiac shadow is probably widened nevertheless. Note clouding of left costophrenic angle.

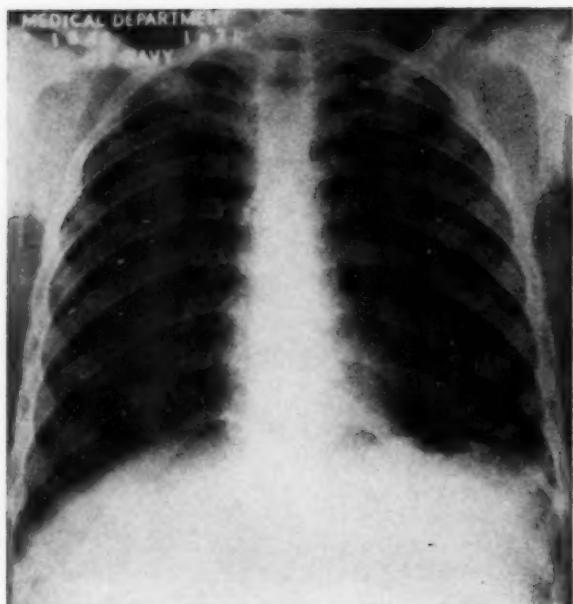


Fig. 3. *Case 1*. Forty-second day of disease—in convalescence. Compare with figure 2.

and rough. Pupils normal. The chest showed diminished breath sounds in the right anterior base, slight dullness to percussion over the right anterior and posterior base, with moist râles in these areas. Some inspiratory wheezes in the left chest. Heart was not enlarged, sounds were poorly heard, but no murmurs noted. Abdomen completely negative. Bilateral partial ankylosis of both elbow joints.

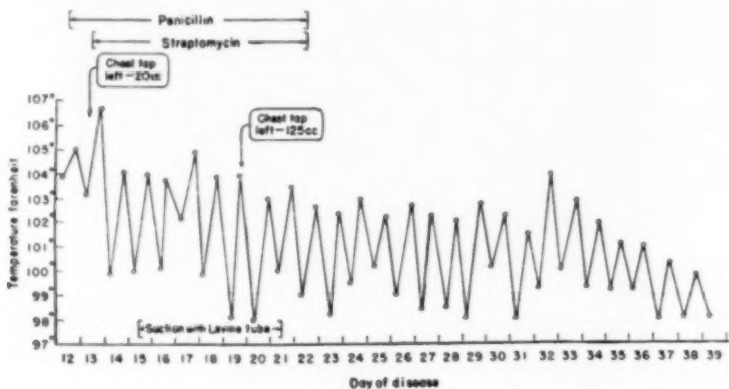


CHART 1. *Case 1*—typhoid fever.

Initial Laboratory Work: Blood culture positive for *Salmonella typhi*. The urine on admission showed ova of *Schistosoma hematobium* in the sediment. The hemoglobin was 8.2 grams (CuSO₄ method), the white blood cells 1,900 with 55 per cent lymphocytes. Culture of the sputum on the first hospital day showed a Type I pneumococcus, a hemolytic, coagulase negative *Staphylococcus aureus*, and *B. coli*, in addition to normal flora.

Course: The patient was started on high doses of penicillin on the first day, and on the second day streptomycin 0.5 gram q. 4 h. was begun. Abdominal distention developed but was controlled fairly well by suction with a Levine tube. The fever remained elevated above 102° F. with spikes to 104 and 105° F. and the patient was extremely ill for the first three hospital days. The chest signs during this time were essentially those of dullness in the bases with prominent high-pitched coarse râles and wheezes. Twenty c.c. of sterile bloody fluid were aspirated from the left chest one day after penicillin had been started. Over the next four or five days the patient showed improvement in his general condition, and the temperature began to swing with wide daily variations. Penicillin and streptomycin were continued for 10 days. On the eighth hospital day 125 c.c. of sterile, grossly bloody fluid were removed from the left chest.

An x-ray on the thirteenth hospital day revealed an enlarged cardiac shadow shifted to the right. This was substantiated by physical examination of the chest. Presence of paradoxical pulse was noted for the first time. Pitting edema of the lower legs and scrotum had been observed about six days previously, so in view of all of these signs, a diagnosis of probable acute pericarditis with cardiac tamponade was made in retrospect.

Over the next two weeks the temperature declined, the chest signs cleared gradually, and there was a shift of the heart back to its normal position and decrease in the size of the cardiac outline.

This case is illustrative of the extent to which pulmonary complications in association with typhoid fever may progress, in spite of early institution of chemotherapy.

CLINICAL SUMMARY FOR CASE 2

History and Physical Examination: An 18 year old Egyptian bootmaker entered the hospital on the eleventh day of an illness which began with headache, fever and colicky abdominal pain. These continued, in addition to diarrhea which developed for several days, as well as cough on the fourth and fifth days. There was a past medical history of relapsing fever two years before, and hematuria one year before. Physical examination on entry showed: Blood pressure 100/70 mm. Hg, pulse 110, respirations 30. Rectal temperature 104.6° F. The patient was short, but moderately well nourished and developed (weight 108 pounds). He appeared acutely ill, but in no distress. Examination of the head gave negative findings. The abdomen was normal. The chest was clear to percussion and auscultation. Remainder of the physical examination was not remarkable.

Initial Laboratory Work: Blood culture was positive for paratyphoid A. The hemoglobin on entry was 11.8 grams (CuSO₄ method); white blood cells 7,600 and normal differential. The urine showed 3 plus albumin and 20 to 30 white blood cells in the sediment. Repeated urine examinations throughout the hospital course continued to show 2 to 3 plus albumin.

Course: Although the patient did not appear seriously ill, the temperature ran daily spiking elevations to between 104 and 105° F. with low points never below 101° F. for the first eight hospital days. For the first two hospital days the chest was completely negative, but on the third day peculiar sticky sounding rhonchi were

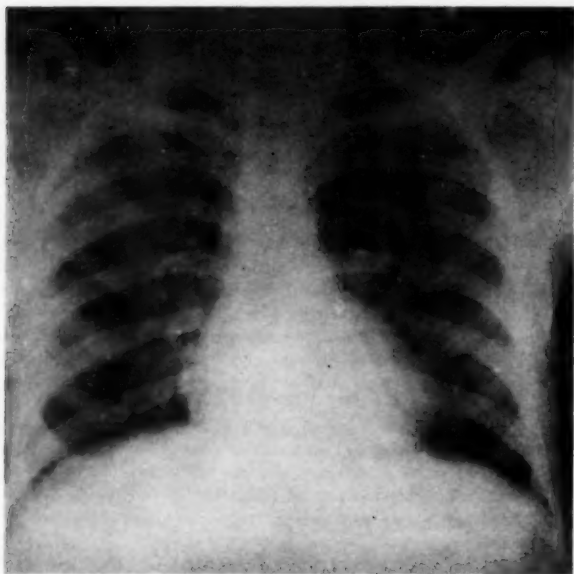


FIG. 4. *Case 2.* Admission film. Note generalized clouding of all lung fields, most marked at right base.

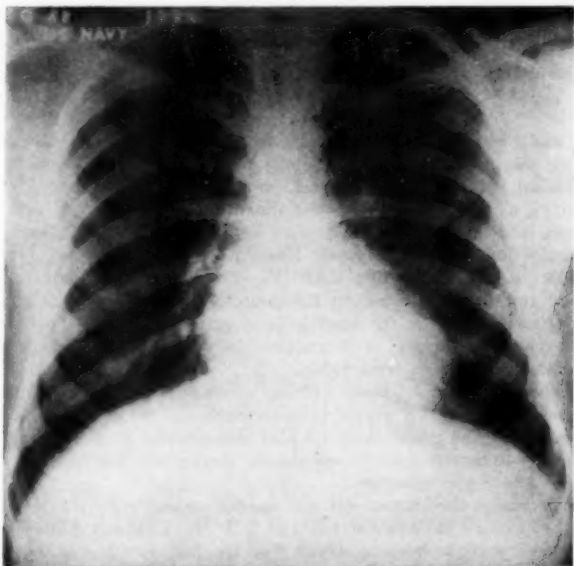


FIG. 5. *Case 2.* Film taken during convalescence. Compare with figure 4.

noted bilaterally in the anterior chest, and in the posterior bases. Prominent high-pitched, harsh rhonchi and squeaks were then heard daily, mainly in the posterior lung bases and in the entire anterior chest bilaterally, for the next nine hospital days. These signs then diminished in degree over a period of two or three days, and finally disappeared completely.

The patient had no cough and produced no sputum in association with the signs in his chest. Aspirated bronchial secretions were cultured on the first, fourth, and tenth hospital days, and again in convalescence. The first culture yielded a non-hemolytic, coagulase negative, mannite positive *Staphylococcus aureus*, but the other cultures grew out only a few colonies of normal throat inhabitants or were sterile.

A chest plate taken on admission showed generalized diffuse clouding which was interpreted as congestive changes, and a homogeneous hazy area in the right base. Subsequent films showed definite clearing of these initial changes, but persistence of accentuated hilar markings.

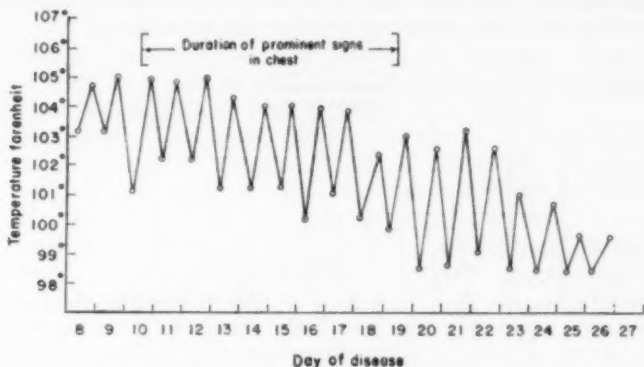


CHART 2. Case 2—paratyphoid A.

The second case is an example of a patient with enteric fever who developed very prominent physical signs in the chest while under observation, without significant bacteriological findings, and with minimal but demonstrable transitory x-ray changes which cleared spontaneously.

CLINICAL SUMMARY FOR CASE 3

History and Physical Examination: An 18 year old Egyptian carpenter was admitted to the hospital on the twelfth day of an illness characterized by chills, fever and headache. The patient denied any previous illnesses when first questioned on entry. Physical examination at that time showed: Blood pressure 108/70 mm. Hg, pulse 88, respirations 20. Rectal temperature 101° F. The patient was thin, but in a fair state of nourishment and development (weight 114 pounds). Examination of the head was negative except for obstruction of both ear canals with wax, which after cleaning revealed large bilateral central perforations of the drums, but no signs of active middle ear disease. The heart was normal. The firm, non-tender tip of a spleen was palpable in the abdomen. The chest exhibited a few rhonchi in the right posterior apex, and moist inspiratory crackles in the right posterior base extending laterally over the right anterior base. Remainder of the examination was without note.

Initial Laboratory Work: The hemoglobin was 12.2 grams (CuSO₄ method), and the white blood cells were 6,650 with 68 per cent lymphocytes. The urine examination gave negative findings. A blood culture was positive for paratyphoid A.

Course: The patient did not appear particularly sick although his temperature spiked daily to about 102° F. for the first seven hospital days before subsiding to normal over another two or three days. On the fourth hospital day very decreased to almost absent breath sounds were noted in the right lower chest, both anteriorly and posteriorly, but mainly in the back. Slight dullness to percussion was also noted in the right lower chest. On the sixth hospital day grunting inspiratory crackles were heard in the right lower chest which were choked off in the end of inspiration. These prominent, "sticky," tight sounding, inspiratory noises which might be called either râles or rhonchi, as well as markedly decreased breath sounds, persisted in the right chest nearly until the patient was discharged. After the temperature had come down to normal the breath sounds began to come through better in the right lower chest, but they were still definitely impaired. When the patient was discharged sticky crackling râles were still present over the right lower chest.

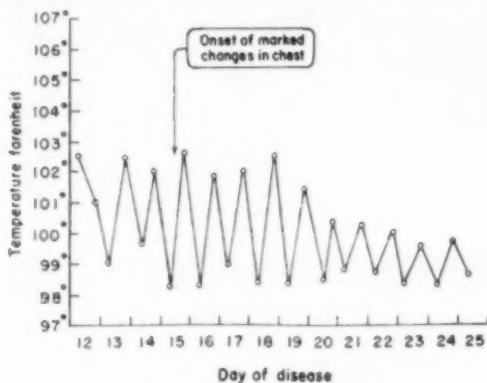


CHART 3. Case 3—paratyphoid A.

Serial chest films during the patient's illness showed a faint wedge-shaped area medially at the right base with multiple mottled shadows and linear streaking. This was interpreted as being suggestive of bronchiectasis. No significant change in the serial films could be detected. Aspirated bronchial secretions on three different occasions showed no significant pathogens when cultured.

Further inquiry into the patient's past medical history several months later brought out the story that the patient had swallowed a small nail at the age of 10 years, which had apparently become lodged in the right lung. At this time he had been sick at home for about three months with cough, sputum, chest pain, but no chills or fever. The nail was finally removed by bronchoscopy, following which the patient brought up small amounts of sputum from time to time, but was otherwise well. The patient stoutly denied any other history of pulmonary disease. When examined nine months after his bout of paratyphoid fever, he still exhibited greatly diminished breath sounds in the right lower posterior and lateral chest, with only a few faint râles. No wheezes, squeaks, groans or any other type of breath sounds were heard in this follow-up examination.

The third case is interesting in that it demonstrates the development in lungs in which a previous lesion was already present, of physical signs which

were very similar to those heard in other cases of typhoid and paratyphoid fevers.

REVIEW OF THE LITERATURE

Frankel⁸ in 1886 was among the first of those who showed interest in the pulmonary manifestations of typhoid fever. He states that "catarrh of the bronchi" occurred in practically every case. He also discussed that form of typhoid in which pulmonary signs and symptoms predominated, which he designated as pneumotypoid. In a later writing Frankel⁹ put the incidence of pneumococcal lobar pneumonia complicating typhoid fever at somewhere between 1 and 7 per cent, in a large number of cases. He was also of the opinion that pulmonary congestion in the presence of a blood-borne disease enabled the organisms to contribute to the maintenance and extension of an inflammatory process by staphylococci, streptococci and other secondary invaders. Frankel believed that the rôle of the typhoid organism itself in producing pneumonia was of secondary importance, although he acknowledged this possibility in rare instances.

Early consideration was also given to the rôle of the typhoid bacillus in pulmonary complications of typhoid fever in this country by Robinson.¹⁰ He reported several cases, one with isolation of typhoid organisms from the sputum as well as in the blood, and his article lists many German and French references dealing with aspects of the same subject in the period before 1900. For example, Chantemesse and Widal¹¹ grew typhoid organisms from the lung at autopsy in several cases and commented upon bronchopneumonia as a specific manifestation; Lepine and Lyonnet¹² attempted to infect dogs with attenuated typhoid organisms by the tracheal route; Stuhlern¹³ isolated the organisms several times from the sputum in typhoid cases; and bacteriological studies on the sputum in 11 typhoid cases with one positive result were published by Edel.¹⁴ In his paper, Robinson concluded that the typhoid bacillus could cause a variety of pulmonary lesions including gangrene, abscess, bronchopneumonia, as well as lobar pneumonia. He also emphasized the likelihood of bloody sputum with typhoid lobar pneumonia.

Stolkind¹⁵ classified some cases of paratyphoid fever as influenzal or respiratory paratyphoid forms of the disease in a discussion of paratyphoid fever before the Royal Society of Medicine in 1915; he believed that these cases represented a definite clinical entity.

Pincsohn¹⁶ in 1921 reviewed the literature and reported one case of paratyphoid fever complicated by pneumonia. He pointed out that the appearance of pulmonary complications was often delayed until after a day or two of normal temperature. He emphasized the need for repeated thorough examinations of the sputum, even in convalescence, if the paratyphoid organisms were to be recovered.

In 1936, Hepple and Holmes¹⁷ described a patient with typhoid fever who developed bilateral patchy bronchopneumonia with blood stained sputum two days after he had become afebrile. *S. typhi* was cultured

repeatedly from purulent sputum but cough plates were negative. The authors recommended passage of sputum through 1:200,000 brilliant green to facilitate recovery of the organisms. The possibility of a broncho-pleural fistula was not mentioned or investigated in the case reported.

A case is reported by Jameson and Signey¹⁸ of purpura and specific bronchopneumonia occurring in an infection due to paratyphoid B. In their case, the organisms were recovered from the lung at autopsy. References are given to similar cases. Bullowa¹⁹ reported a case of typhoid fever with roentgen-ray and physical signs of left upper lobe pneumonia, but no bacteriological studies were made.

A patient with paratyphoid B who had physical signs and x-ray evidence of bilateral pneumonic patches is described by Hogarth.²⁰ Proof as to the etiologic organism is lacking.

Hodgson²¹ in 1945 mentions lobar pneumonia as a complication in five cases out of 84 typhoid and paratyphoid patients observed. He also reports that about half of the total cases had severe cough.

Although diseases caused by all members of the *Salmonella* group of organisms do not strictly come into the province of this discussion, the incidence of pulmonary complications reported in association with *Salmonella suispestifer* infections is deserving of mention. About one-third of Harvey's²² 21 cases had definite evidence of pulmonary or pleural involvement. In another series of six cases described by Jager and Lamb,²³ five showed clinical or x-ray signs of pulmonary involvement, but in none were the organisms recovered from the sputum.

Surgical complications, such as empyema and costal chondritis, have been recently discussed by Minor and White.²⁴ Harvill²⁵ has reported a case of lung abscess due to typhoid, and lists similar cases reported by others.

Ingegno, D'Albora, et al.²⁶ have reported very recently an outbreak of *Salmonella montevideo* gastro-enteritis, in which note of bronchopulmonary involvement was made in 6 per cent of 350 affected. An interval of quiescence with normal temperature between the phase of gastro-enteritis and the pulmonic phase was present in about half of those who developed pulmonary signs. In only one case was *S. montevideo* recovered from the sputum. X-ray findings of a patchy or diffuse pneumonitis were present in eight out of 15 cases studied. On the basis of physical signs encountered, the main changes were thought to be those of bronchial inflammation. In explanation of pulmonary findings the authors considered the possibility of etiologic association with a virus infection, or the toxic or allergic effects of the *Salmonella* organism.

DISCUSSION

A primary pneumonia in which the etiological agent is one of the enteric group of *Salmonella* organisms is relatively rare. Meningococcal, anthrax, and brucella infections are examples of diseases in which a pneumonic form

may be seen in rare instances. In the series of 80 patients who made up this study, there was no case of primary typhoid or paratyphoid pneumonia.

It is only reasonable to expect the occurrence of secondary pneumonia in diseases such as typhoid and paratyphoid fever. The disease is often severe, the patient may be delirious or stuporous, or in a state of collapse, providing ample opportunity for pulmonary stasis or aspiration. Under such circumstances a terminal pneumonia is possible, the pathological features of which have been described by Moon.²⁷ Responsible organisms may be one of the pneumococci, or a mixture of the normal flora found in the upper respiratory tract. Of the nine patients with pneumonia in this report, pneumococci seemed to be the cause in two cases. There is no evidence that the enteric fevers show any special predisposition to invasion of the lungs by pneumococci.

The pneumonia which occurs late in the disease or in convalescence has been mentioned in the literature. Two such cases reported here were of this type. The etiology of this late pneumonia in typhoid and paratyphoid fevers remains obscure.

As has been noted above, the pulmonary complications in the enteric fevers, with the exception of pneumonia, have been slighted in the modern literature. The studies reported in this paper emphasize the frequency of pulmonary signs other than those due to pneumonia; these demand renewed appreciation and explanation. The high incidence of physical signs was not accounted for by pneumonia, because if those cases in which pneumonia occurred are excluded, it still leaves approximately one-third of the entire group with moderate or prominent signs in the chest. The characteristics of the signs elicited were mainly those associated with bronchial changes.

No satisfactory explanation for the bronchitis of typhoid fever has yet been offered. The terms hypostasis and pulmonary congestion have been loosely used but without any specific basis. Positive physical signs in the group studied were not confined to those patients most severely ill. Furthermore, many of the paratyphoid A patients displayed an amazing absence of toxicity and were rarely prostrated by their disease even though they ran a high fever. Yet, these patients exhibited pulmonary signs just as frequently as did the typhoid patients. Rhonchi, wheezes, squeaks, and harsh breath sounds clearly indicate bronchial involvement, and are not the type of findings one could expect from pulmonary congestion and stasis. In addition, signs of pulmonary congestion are usually heard in the lower lungs while most of the altered breath sounds reported here were heard throughout the lungs.

What then are the factors operating which might account for a specific mechanism of bronchial involvement? The bacteriological results in this study showed no consistent association with bacterial pathogens. Ingegno, D'Albora, et al.²⁸ on the basis of their cases suggested the possibility that allergic effects of the *Salmonella* organism might be responsible. A point

against this contention is the fact that eosinophiles were conspicuously absent in smears of bronchial secretions in patients studied,⁶ although it should be remembered that eosinophiles are depressed in the peripheral blood in the enteric fevers.

It seems likely that the bronchial changes reflect injury to the bronchial epithelium of a structural or functional nature, initiated either directly or indirectly by the underlying disease. Such injury could be to ciliary function, or damage to the bronchial wall itself. Further investigation along the line of cellular injury produced by the endotoxins of the enteric organisms might be worthwhile in this regard, since Morgan²⁸ has described cell destruction of various tissues in animals resulting from intravenous administration of a toxic somatic antigen derived from the typhoid bacillus.

SUMMARY

1. Eighty cases of typhoid and paratyphoid fevers occurring in Egyptian males are classified as to degree and type of pulmonary signs which were found during the disease course.
2. Pulmonary signs were noted in 64 per cent of the entire series, and signs of moderate or prominent degree occurred in 42 per cent.
3. Signs most frequently elicited were râles, rhonchi, decreased breath sounds, squeaks, dullness and wheezes in that order. These tended to occur in combination with each other.
4. Frank pneumonia was found in 11 per cent of the cases.
5. Bacteriologic studies of bronchial secretions and sputum in 19 patients failed to reveal any constant pathogens which could be related etiologically with the pulmonary signs.
6. Particular features of pulmonary involvement in the enteric fevers are illustrated by three case reports.
7. The literature pertaining to typhoid and paratyphoid pulmonary complications is briefly reviewed.
8. The high incidence of signs suggesting bronchial involvement in the series studied is emphasized, and possible explanations for their occurrence are discussed.

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PRESENT RÔLE OF THE ARTIFICIAL KIDNEY IN CLINICAL THERAPY *

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ALTHOUGH earlier efforts at the production of an apparatus for the extracorporeal dialysis in blood had met with some success, it remained for Kolff¹ in Holland and, simultaneously, Murray² in Canada to perfect the first apparatus for effective clinical use. Since that time modifications of these devices have been constructed and used by others in this country and Europe.^{3,4} Our experience has been with a modified form of the Kolff apparatus which we have used for the past two years in a series of 120 clinical trials. Modifications of the technic and new devices described elsewhere^{5,6} have increased the efficacy and decreased the risk to the patient as well as the undesirable side reactions to a point where such a technic may be widely employed where the removal from the blood or the addition to it of diffusible substances may be indicated. This increase in scope has become apparent in the application of the procedure to a variety of clinical situations, many of which are as yet incompletely explored. At the present time, however, enough data have accumulated to indicate that it may be of value in the situations listed below.

1. *Acute Renal Insufficiency*: While conservative measures of therapy have progressed to the point where the mortality in the lower nephron syndrome has greatly decreased,⁷ there nevertheless are cases of potentially reversible renal disease in which the removal of large amounts of nitrogenous wastes and correction of electrolyte imbalance may be life-saving. Patients who develop acute renal insufficiency following difficult and prolonged surgery, or whose anuria is precipitated by severe trauma, fall into a different clinical category from the previously healthy individual whose anuria is a result of carbon tetrachloride inhalation or a mismatched transfusion during elective surgery. To the latter a convalescence complicated by azotemia and acidosis may not necessarily be hazardous. To the elderly, debilitated, postoperative patient recovery from major surgery complicated by two weeks of semi coma, vomiting and immobility may be difficult. Here the use of an artificial kidney, even in situations which would eventually respond to conservative therapy, may prove an effective adjunct to the usual

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methods employed. The amelioration of nausea and vomiting, the increased well being and alertness which accompany dialysis greatly facilitate medical management. These effects permit earlier mobilization of debilitated post-operative patients and enable patients with uncomplicated anuria to maintain a state of reasonable well being for periods of 14 or 15 days. Optimum conservative therapy depends upon the provision of adequate calories in the form of fat and carbohydrate to decrease endogenous protein breakdown and minimize the liberation of non-protein nitrogen, acid metabolites, and potassium. If adequate calories can be supplied, recent work has indicated that small amounts of the essential amino acids may further decrease body protein catabolism in post traumatic states.⁸ To supply these substances in

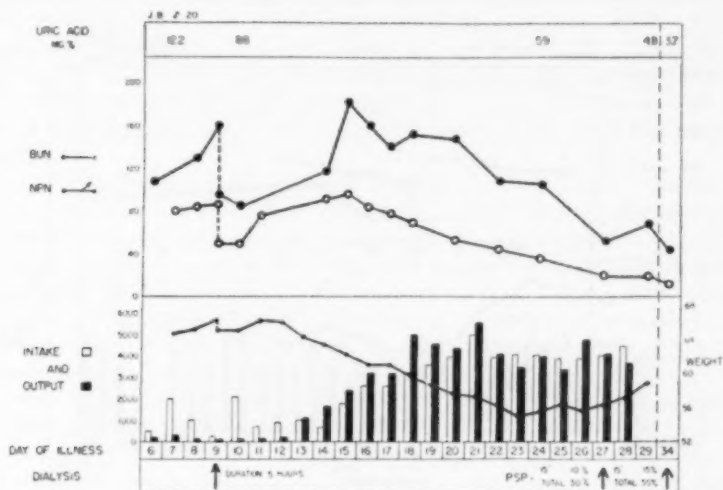


FIG. 1.

adequate amounts by parenteral administration is a virtual impossibility because of the volume of fluid in which they must be administered. The ingestion of such substances has a physiologic advantage and in addition enables the patient to obtain an adequate total caloric intake in the small volume of fluid dictated by the inability to form urine. Such therapy, however, depends upon the ability and willingness of the patient to eat and drink, and frequently the patient with anuria of more than short duration is drowsy, nauseated and uncoöperative. Improvement in these symptoms following hemodialysis makes possible improved conservative management. For this reason it has been our practice to employ hemodialysis with the artificial kidney in patients whose anuria has lasted for more than seven days, or whose clinical status is in doubt for any other reason. On this regime

a recent patient remained semi-ambulatory throughout her course and ingested and retained over 1500 calories on the thirteenth day of her acute renal insufficiency.

In contrast is the course of another, earlier patient shown in figure 1. This patient who had been previously healthy prior to intravascular hemolysis and renal shutdown, was nauseated, apathetic and semi-comatose on the day of dialysis. His total intake was by the parenteral route. Following dialysis the loss of nausea and the increased alertness made possible maintenance by the oral route from then until discharge. It should be noted also that with the onset of diuresis nitrogen retention actually increased as it does in such cases, so that seven days following the beginning of a daily urine output of over one liter, the non-protein nitrogen level was as high as on

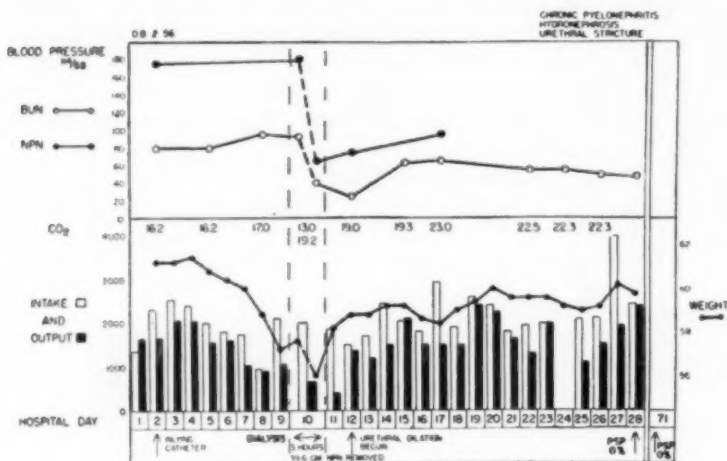


FIG. 2.

the day of dialysis. It is probable that a further increment in non-protein nitrogen was spared by removal by the artificial kidney. There is no question but that this previously healthy young adult would have survived without dialysis. There is equally little doubt in the minds of those who observed his clinical course that it was greatly improved by use of the artificial kidney.

2. *Preparation of the Chronic Uremic Patient for Surgery:* The beneficial effects of dialysis in the chronic uremic patient prior to surgical procedures have been of value in several instances. The trauma of surgery may be accompanied in patients with renal insufficiency by increasing azotemia and debility. Frequently such surgical procedures are aimed at the improvement of renal function or the prevention of further damage thereto. The preparation of such patients by the adjustment of chemical imbalance

may facilitate their post-operative course and their tolerance for the operative procedure. Such patients may also require dialysis following surgery to minimize the effects of the temporary aggravation of renal dysfunction secondary to major surgery. Figure 2 illustrates the preoperative use of such a procedure in a patient with chronic pyelonephritis, hydronephrosis and urethral stricture. Following the placement of an inlying catheter, this patient's clinical situation markedly deteriorated, azotemia increased somewhat, and acidosis was aggravated. On the morning of dialysis he was almost completely comatose and appeared critically ill. Following five hours of therapy with the artificial kidney there was marked chemical and clinical improvement. Forty-eight hours later urethral dilation was begun and the patient was discharged 16 days later ambulatory. He continues to carry moderate elevations of blood urea nitrogen, but these are not inconsistent with his working five days a week at a sedentary job. While in all probability this patient also with conservative management might have eventually achieved the same result, there can be no question but that the use of hemodialysis in this situation facilitated and shortened his hospital course.

3. Rehabilitation of the Chronic Uremic Patient: While removal of nitrogenous wastes in the patient with severe chronic renal insufficiency may be rapidly followed by return to the previous levels, nevertheless in certain such patients the increase in well being and in appetite may facilitate intensive dietary therapy in such patients and shorten their hospital stay. Since the end to be achieved by dietary therapy may be attained more rapidly and efficiently with the use of the artificial kidney, its application in selected cases may be useful. Particularly useful is the correction of acidosis by the removal of acid metabolites in the chronic uremic patient with moderate oliguria and compensated hypertensive cardiovascular disease. In such patients acidosis is not due primarily to excess base loss, in contradistinction to the polyuric patient, and the cardiovascular disease and oliguria make dangerous and ineffective the administration of large amounts of sodium in an attempt to correct acidosis. In such situations the correction of acidosis may be achieved by the removal during hemodialysis of retained acid metabolites. The correction of these abnormalities is followed by improvement in appetite and general well being. In patients with severe renal insufficiency this may be transitory, but in several the duration of improvement has been of some prolonged value. Until recently, uremic patients with severe hypertension have not responded well to dialysis. Recent investigations into the mechanism of the pressor response accompanying dialysis, and osmotic changes secondary thereto have aided in eliminating the vascular response of such hypertensive patients and enabled us to employ the technic in such patients with favorable results.

4. Special Indications: (1) The patient with acute anuria is prone to several serious complications during the course of a disability which is essentially reversible. Of these, acute spontaneous potassium intoxication

is one of the most serious. Death from toxic concentration of potassium in the extracellular fluid may result within several hours after the onset of clinical symptoms. This situation, as is the underlying disease process, is

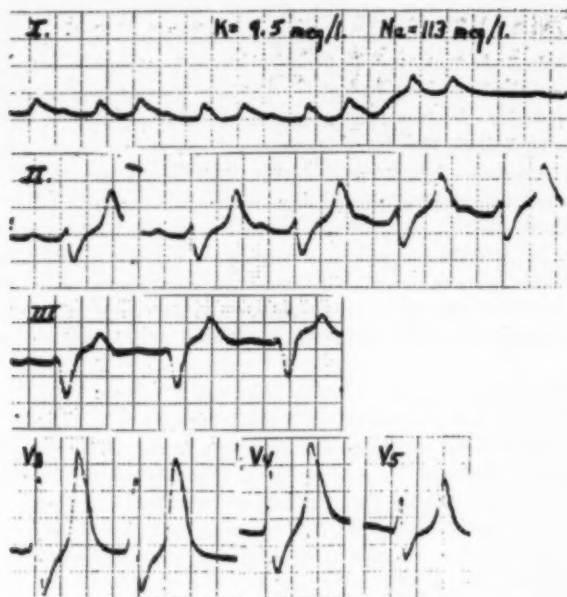


FIG. 3a. Patient, age 35, with acute potassium intoxication. Before dialysis.

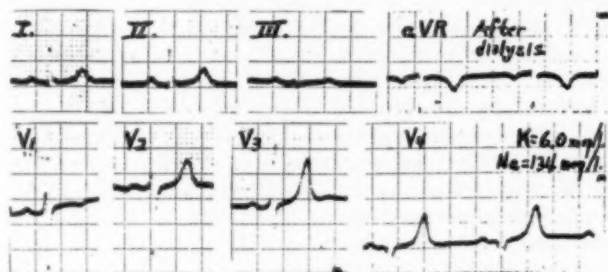


FIG. 3b. Patient, age 35, with acute potassium intoxication. After dialysis.

amenable to proper therapy. It has been shown that the most effective method for the treatment of this acute medical emergency is dialysis with the artificial kidney.⁹ The effect of hemodialysis in rapidly removing excess potassium from extracellular fluid and correcting acidosis may cause total

disappearance of the signs and symptoms of potassium intoxication. In the face of continuing anuria this procedure is more rapidly effective and of far greater duration than other methods of therapy. Figure 3 illustrates such a case and shows the marked changes in the typical electrocardiographic pattern of potassium intoxication which results from effective dialysis.

(2) A second complication of acute anuria which may have serious consequence is acute pulmonary edema. This may result from injudicious administration of excess fluid or as recent evidence indicates¹⁰ may be secondary to a toxic effect of severe azotemia and chemical imbalance upon myocardial function. Three cases with acute pulmonary edema occurring in the course of acute renal insufficiency have been treated by hemodialysis with definite evidence of improvement. Although the mechanism by which

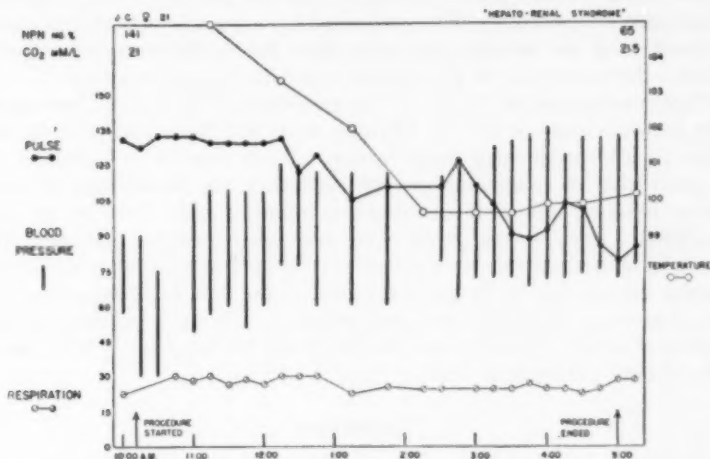


FIG. 4.

this is accomplished is not at present clear, it is probably a combination of dehydration and correction of severe chemical imbalance.

(3) Occasionally following the onset of diuresis in a patient whose previous acute renal insufficiency is the result of prolonged shock-like state, anoxia or both, the resumption of urinary output is accompanied by selective resorption of sodium and chloride.¹¹ Such patients may have severe central nervous system symptoms, particularly disturbances of the psyche. In two such cases the removal of excess sodium by dialysis has resulted in clinical improvement. Contrary to the common concept of sodium and chloride loss during diuresis subsequent to lower nephron nephrosis, such patients selectively retain these electrolytes, and this syndrome in patients with anuria as a result of clinical situations described above, or in patients with liver disease, must be looked for.

(4) Acute renal insufficiency complicated by evidence of acute hepatic insufficiency results in a clinical syndrome which presents a more complicated problem than so-called "pure" lower nephron nephrosis. Such patients may present the picture previously described under the term "hepatorenal syndrome" in which hyperpyrexia and hypotension refractory to replacement therapy are major constituents. The patient with concomitant liver disease and anuria is more critically ill and his response to dialysis is more dramatic. Such cases present a special indication for the procedure. In addition, in several cases, the elicitation of a pressor response during dialysis has been of marked benefit in correcting severe hypotension refractory to other methods of therapy. Figure 4 illustrates such a case in which 4000 c.c. of whole blood administered 48 hours prior to dialysis had failed to raise systolic blood pressure above 90 mm. of mercury and who prior to dialysis was in pulmonary edema. The mechanism by which this pressor response is produced is at the present time not clear, but preliminary investigation indicates the production of an increase in cardiac output as a factor.

Contraindications to the use of this procedure at the present time appear to be patients who are actively bleeding from any focus and patients with severe rapidly progressing hypertension. Since heparin is necessary for the prevention of coagulation in the apparatus, the possibilities of spontaneous bleeding following anticoagulant administration is to be seriously considered. In the second group it has been our experience that the clinical picture in uremic patients with severe rapidly progressing hypertension and vascular disease may be in great part due to the vascular disease and very little dependent upon their nitrogen retention. In such patients the restoration of serum values to near normal levels has resulted in little change in the clinical picture or prognosis.

SUMMARY

In its present status the use of the so-called "artificial kidney" has definite therapeutic value in a number of clinical syndromes. Its use may be imperative in acute complications of acute anuria such as potassium intoxication and pulmonary edema. It appears to have value as an adjunct to conservative therapy in prolonged uncomplicated anuria. The preparation of the chronic uremic patient for surgery and the rehabilitation of the chronic nephritic are possibilities which may have value in properly selected cases. In less frequent and less well defined situations concerned with renal insufficiency, particularly those associated with hepatic damage, hemodialysis may be effective. Simplification of the technic by future developments may make it of widespread general value.

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ADDICTION TO BARBITURATES AND THE BARBITURATE ABSTINENCE SYNDROME*

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THE purpose of this paper is to point out that chronic intoxication with barbiturates represents a true addiction—no matter how addiction is defined—and to describe the manifestations of maintained intoxication with barbiturates as well as the signs and symptoms which occur following withdrawal of these drugs from chronically intoxicated individuals.

The increasing incidence of acute intoxication with barbiturates is unquestioned. Production of the barbiturates in the United States has increased 400 per cent since 1933. In 1948, over 300 tons of these drugs were manufactured.¹ Acute intoxication with barbiturates accounts for about 25 per cent of all cases of acute poisoning admitted to general hospitals² and more deaths are caused by barbiturates, either accidentally ingested or taken with suicidal intent, than by any other poison.^{3, 4, 5, 6} The number of deaths due to barbiturate poisoning has increased 300 per cent since 1940. The large number of papers which have appeared in the medical literature on barbiturate poisoning and its treatment reflect the rising incidence and seriousness of the problem.

Although much less attention has been paid to chronic intoxication with barbiturates than to acute intoxication, there is evidence that chronic intoxication with barbiturates is increasing. This includes the increased incidence of chronic barbiturate intoxication among morphine addicts admitted to the United States Public Health Service Hospital at Lexington, Kentucky, the increased number of requests received at that institution concerning the manifestations and treatment of the condition, and the increased number of tips investigated by agents of the Bureau of Narcotics which prove to be cases of addiction to barbiturates and not of addiction to morphine. Officials of both Federal and State Food and Drug Administrations^{6, 7} have records of prescriptions for barbiturates which have been refilled hundreds of times. These officials also state that the illegal sale of barbiturates by unscrupulous pharmacists and by "goof-ball" salesmen is quite common.

The relative neglect of chronic barbiturate intoxication in the medical literature has probably been due to the erroneous impression, which has been widely held in both the United States and England, that abstinence symptoms did not follow abrupt withdrawal of barbiturates from chronically

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intoxicated persons. These drugs were, therefore, not believed to be addicting.^{8, 9, 10, 11} In recent years this mistaken concept has been shaken by the appearance of reports of convulsive seizures following withdrawal of barbiturates.^{12, 13, 14, 15} The Germans have long recognized that withdrawal of barbiturates from persons addicted to these drugs may be followed by the appearance of convulsions and/or a psychosis which resembles alcoholic delirium tremens.^{16, 17, 18, 19} In recent experiments, Isbell and his collaborators administered pentobarbital, seconal and amytal to former morphine addicts for three to five months.²⁰ Following withdrawal of the drugs from these patients, four of the five subjects developed convulsions and four of the five became psychotic. This experiment was important since it showed that the symptoms of abstinence from barbiturates were not due to a combination of intoxications, to malnutrition, or to a preëxisting psychotic or epileptic diathesis.

ETIOLOGY OF BARBITURATE ADDICTION

As in alcoholism or narcotic drug addiction, the most important factor which predisposes to addiction to barbiturates is the presence of a personality defect. Although not as many data are available on the personality types of barbiturate users as on the personalities of morphine addicts, there appear to be no fundamental differences between these two groups of individuals.^{18, 20} Individuals with various kinds of psychoneuroses or character disorders (constitutional psychopaths) are very likely to become addicted to barbiturates—or any other drug—if introduced to it under proper circumstances. Many psychoneurotics become addicted to barbiturates as a result of the prescription of these drugs for insomnia. Characteristically, psychoneurotic patients maintain their dosage at low levels for considerable periods of time. When psychoneurotics do begin to elevate the dose they increase it rapidly and, as Pohlisch has said, the drug is changed from a means of inducing sleep to a means of producing intoxication.¹⁷ Psychopaths begin the use of the drug in order to experience the intoxicating effects rather than to induce sleep. They, therefore, raise their doses very rapidly from the very onset of addiction and usually take as much as their inherent tolerances will permit.

In contradistinction to the situation in narcotic drug addiction, a large proportion of the cases of chronic barbiturate addiction result from administration of the drugs by physicians. This situation probably reflects the mistaken idea that the barbiturates are not addicting drugs.

Addiction to other drugs predisposes to addiction to barbiturates. Morphine addicts will use these drugs when they are unable to obtain morphine and frequently take them with morphine in order to reinforce the effect of the opiate. Alcoholics are likely to begin the use of the drugs to relieve the nervousness following a long debauch. They find that the effects are similar

to those of alcohol and continue the use of barbiturates to induce intoxication rather than to relieve nervousness or insomnia.

TYPES OF ABUSE OF BARBITURATES

The potent short-acting barbiturates—pentobarbital, seconal and amytal—are most popular with barbiturate addicts. The less potent long-acting drugs—barbital and phenobarbital—are less commonly used. The drugs are usually taken orally. Morphine addicts occasionally inject them intravenously. Due to the irritating properties of these compounds, subcutaneous injection is almost impossible as abscess formation will occur whenever the drugs are so administered. Like alcohol, addicts may use the drugs for short sprees lasting only for one night or a day or so, for long debauches of several weeks' duration, or they may take the drugs continuously for months or years. Use of barbiturates to reinforce the effects of alcohol is quite common and many psychopaths are introduced to barbiturates in this way. Some individuals abuse barbiturates and benzedrine concomitantly. This practice is reminiscent of the conjoint use of morphine and cocaine by narcotic drug addicts.

THE CLINICAL PICTURE OF BARBITURATE INTOXICATION

The signs and symptoms of chronic barbiturate intoxication are identical with those of moderately acute intoxication.²⁰ The phenomena observed are predominantly due to the effects of the drugs on the central nervous system and may be divided into mental and neurological signs.

The mental signs of chronic barbiturate intoxication include impairment of intellectual functioning, confusion, poor judgment, depression, melancholia, and psychic regression. Individuals addicted to these drugs neglect their appearance, become unkempt, dirty, do not shave and wear clothes soiled with food which they have spilled. They have difficulty in performing simple tasks or in carrying out simple psychological tests. They are irritable, morose and quarrelsome. Their judgment is so impaired that, even when they are so intoxicated that they are unable to walk, they will continue to take more and more drugs. This condition has been termed automatism and may lead to death. They are careless with cigarettes and are quite likely to start serious fires. They become so depressed that suicide is a distinct possibility. They regress to an infantile level, have to be waited on, fed and nursed. Emotional control is impaired and they are likely to fight over minor incidents or fancied insults. Some addicts become hostile and develop mild paranoid ideas.

True toxic psychoses seldom occur during maintained chronic intoxication with barbiturates. The addicts are usually oriented in time, place and person and seldom have hallucinations or delusions. When toxic psychoses

do occur they are usually due to superimposition of an acute barbiturate intoxication on the preëxisting chronic condition.

Spectacular neurological changes are present during chronic barbiturate intoxication. These may suggest organic diseases of the nervous system such as Parkinsonism, multiple sclerosis, cerebellar brain tumors and general paresis.⁸ The signs observed include ataxia in gait and station, dysarthria, nystagmus, adiadokokinesis, hypotonia, tremor, decrease in the abdominal reflexes, and occasionally transient ankle clonus and Babinski signs. The deep tendon and corneal reflexes are usually unchanged unless an acute intoxication is superimposed on the chronic state. There are no sensory changes.

Barbiturate addicts who take no other drug usually maintain a good state of nutrition and differ in this way from alcoholics and from most narcotic drug addicts. Pulse rate, blood pressure, respiratory rate and temperature are usually altered only slightly.

Even with very short-acting barbiturates such as seconal, cumulation of drug effects occurs if the addict takes several doses of the drug daily. The effects of the drugs vary markedly in the same individual from day to day.²⁰ Doses which one day cause acute intoxication and even coma will on another day produce only mild signs of intoxication. This variation in effect, like the variation in the effects of alcohol, is partially related to food intake. The effects of the drug on the mood of the addict are also variable and appear to depend to some extent on the emotional cast of the individual on any particular day. On some days an addict will be garrulous, happy, and will enjoy himself. On another day he may be downcast, weeping, and complaining about his wasted life. Like alcohol, barbiturates appear to accentuate the basic personality pattern. Extroverted individuals usually are euphoric, talkative and humorous. Shy persons become even more withdrawn and schizoid and the mood swings become even greater in cyclothymic persons.

During chronic barbiturate intoxication the electroencephalogram reveals an increased percentage of waves with frequencies of 15 to 30 per second (beta waves). Early in addiction to barbiturates, large slow waves resembling normal sleep waves are seen but these disappear as addiction proceeds.

Persons addicted to barbiturates develop partial tolerance to the sedative and hypnotic effects of the drug.^{17, 18, 20} In fact, individuals who use these drugs sleep only an hour or two more per day than they do normally. The degree of tolerance to the hypnotic effect of barbiturates is, however, not nearly so great as that which is developed against the sedative effect of the opiates. It is probable that no tolerance can be developed to the lethal effect of these drugs so that the ingestion of a very large dose of barbiturates by an individual addicted to barbiturates is just as likely to result in death as is ingestion of the same dose by a person who is not addicted to these drugs.

THE BARBITURATE ABSTINENCE SYNDROME

Signs of abstinence from barbiturates may appear after sudden reduction of the dosage of barbiturates which the addict is accustomed to taking as well as after complete and abrupt withdrawal of the drugs. The barbiturate abstinence syndrome never develops as long as the addict continues to ingest his usual dosage of barbiturates.

In the first 12 to 16 hours after abrupt discontinuation of medication, the patients appear to improve. Their thinking and mental status become clearer and most of the neurological signs of intoxication disappear. As the signs of intoxication decline, the patients become apprehensive and so weak that they can hardly stand. Fasciculation of various muscle groups and a coarse tremor of hands and face become evident. The deep reflexes are hyperactive and slight stimuli may cause excessive muscular responses. The patients cannot sleep, are nauseated, have abdominal cramps and may vomit frequently. They may lose as much as 5 kg. (12 lbs.) of body weight in the first 36 hours of abstinence. This weight loss is due to loss of body water by all routes and to decreased intake of fluid. Concomitantly, elevation of the non-protein nitrogen content of the blood, hypoglycemia and hemoconcentration appear. These signs are probably attributable to dehydration. Blood pressure and pulse and respiratory rates are increased. Patients develop difficulties in making cardiovascular adjustments on standing. The pulse rate rises 40 to 80 beats per minute. The systolic blood pressure, while fluctuating widely, falls 15 to 50 mm. of mercury while diastolic blood pressure increases. The pulse pressure is therefore narrowed. These cardiovascular phenomena, unlike those seen in normal individuals, become more marked the longer the patient stands. They are not similar to those seen in postural hypotension in which both systolic and diastolic blood pressure decrease and in which the normal increase in the pulse rate fails to occur. This disturbance of cardiovascular physiology resembles the derangement seen during or after many severe illnesses, particularly acute infectious diseases. No clinical or electrocardiographic evidence of myocardial damage is present. Anxiety, tremor and weakness continue to increase. Between the sixteenth hour and the fifth day of withdrawal, but usually about the thirtieth hour, one or more grand mal convulsions, which are indistinguishable from those occurring in idiopathic epilepsy, occur. Following the convulsions, patients usually regain consciousness within a few minutes. They may be confused for an hour or two but prolonged stupor such as follows grand mal convulsions due to idiopathic epilepsy is seldom seen. Generally, patients have no more than three major convulsions but numerous minor episodes, which are characterized by clonic twitching without loss of consciousness, or by writhing athetoid movements of the extremities, may occur before, between, or after the major convulsions. Paroxysmal bursts of high voltage waves of slow frequency appear in the electroencephalogram. These can usually be detected before the major con-

vulsions occur and may be present after the convulsive phase of abstinence is past. Electroencephalograms obtained during convulsions due to abstinence from barbiturates are identical with electroencephalograms obtained during convulsions due to idiopathic epilepsy. Following the convulsions, large slow stupor waves appear, but these disappear as clouding of the patient's consciousness declines. After the convulsive phase is over, an increased number of waves of frequencies of 6 to 7 per second may be observed for 7 to 14 days. Thereafter the electroencephalographic pattern is indistinguishable from that of normal people. Between or following convulsions, patients continue to exhibit anxiety and other symptoms. Unless the patient becomes psychotic, these symptoms gradually disappear and, after two or three weeks, patients have usually recovered completely.

Whether or not convulsions occur, barbiturate addicts are likely to become delirious, usually between the third and seventh days of abstinence. The onset of the psychosis is often heralded by insomnia of 24 to 48 hours' duration after which the patients begin to experience hallucinations and delusions. Both visual and auditory hallucinations occur but the former are much more prominent. The patients become disoriented in time and place but ordinarily not in person. The delirium is likely to appear and be worse at night. The hallucinations resemble those observed in delirium tremens. The patients may see little people, giants, absent relatives, animals, insects, birds, snakes, fish, etc. They may believe that imaginary persons are trying to harm them. They frequently misidentify objects, persons and noises. They have a marked tremor and, after the psychosis appears, develop fever and even greater elevations of blood pressure and pulse and respiratory rate.

The emotional reaction to the psychosis appears to be influenced by the basic personality characteristics of the patient. Some individuals become extremely agitated, try to fight and escape from their imaginary persecutors and may become dangerously exhausted. Other patients lie quietly, watch their strange visitors and listen to imaginary music without taking any action. Some patients are so quiet that, even though they are having hallucinations, the psychosis may not be detected unless specific inquiries about symptoms are made. The psychosis may also resemble schizophrenia. The patients may show mutism, bizarre affect, have ideas of control and influence, build up a system of paranoid delusions and experience sexual hallucinations.

Even if not treated, patients will usually recover from the psychosis within two weeks of its onset. Some patients recover within three or four days and some require two or three months. Improvement generally begins with the return of the ability to sleep. After hallucinations are no longer present, patients may, for a few days, be under the delusion that their hallucinations were real.

The barbiturate abstinence syndrome varies considerably from patient to patient. Some individuals escape without experiencing more than weak-

ness and anxiety. Others may have convulsions but not a psychosis. Some do not have convulsions but develop a delirium, and some patients may have both convulsions and a psychosis.

ILLUSTRATIVE CASE REPORTS

Case 1. A 48 year old male was admitted to the United States Public Health Service Hospital, Lexington, Kentucky for the fifth time on December 26, 1946. He had used narcotic drugs since 1915 and had been withdrawn about 10 times but never remained abstinent for more than a few months following discharge from various institutions. On admission he was groggy, confused, ataxic and had dysarthria and nystagmus. He gave a history of taking 7 grains of morphine intravenously and 20 pentobarbital capsules orally each day during the past two years. Physical examination was negative except for numerous abscess scars, tattoo marks over the veins and a kyphosis in the region of the fifth and sixth dorsal spines. On previous admissions the kyphosis had been shown to be due to partial collapse of the fifth and sixth dorsal vertebrae and was interpreted to be a result of trauma rather than of tuberculosis. On the basis of psychiatric examinations done on previous admissions, he had been classed as having a character disorder (constitutional psychopathy). There was no familial history of epilepsy or insanity. Laboratory data on present and preceding admissions were not remarkable. There was no history of syphilis and Kahn and Wassermann reactions have been repeatedly negative.

Following admission the patient was placed on pentobarbital 0.1 gram four times daily and on methadone 10 mg. four times a daily. On December 28, at 9:45 a.m. approximately 36 hours after admission, the patient developed a major convulsion and fell forward striking his head on the floor. Following the convulsion, 0.5 gram of sodium amytal was administered intravenously, and the dosage of pentobarbital was elevated to 0.2 gram four times daily. X-ray of the skull was negative for evidence of fracture. On the following day the patient was confused, disoriented in time and place and had both visual and auditory hallucinations. He was transferred to the psychiatric service where positive Babinski and Kernig signs and fever of 101° F. were observed. Lumbar puncture was performed. Spinal fluid was grossly bloody but the pressure and dynamics were essentially normal. On the following day the patient continued disoriented in time and place but not in person. He was untidy, dirty and uncoöperative. He talked with non-existent people and appeared to be having very frightening hallucinations. He was given sodium amytal 0.5 gram intramuscularly three times daily, plus 1.0 gram of sulfadiazine and 2.0 grams of sodium bicarbonate every four hours. Under this regime the psychosis gradually cleared and, three days later, the patient appeared to be completely rational. On January 3, 1947 the dosage of sodium amytal was reduced to 0.5 gram intramuscularly once daily and 0.2 gram of pentobarbital orally four times daily. On January 6, 1947 his medication was changed to 0.2 gram of pentobarbital orally at 10 a.m. and 9 p.m. On January 13, 1947 the dosage was reduced to 0.1 gram of phenobarbital at 10 a.m. and 9 p.m. On January 19, 1947 all medication was discontinued. The patient was kept on the psychiatric ward until May for further observation. On February 23, the electroencephalogram revealed the presence of abnormal slow waves which were maximal over the frontal region. Further examinations of spinal fluid were negative and a pneumoencephalogram, which was performed in March of 1947, was also negative. The patient was discharged in May, apparently completely well.

Comment: This case represents an example of convulsions occurring following sudden reduction of addict's accustomed dosage of barbiturates.

The patient incurred a severe head injury as a result of his convulsion and developed a subarachnoid hemorrhage. It is difficult to decide whether the psychosis was due to the subarachnoid hemorrhage or to abstinence from barbiturates.

Case 2. A male 50 years of age was admitted to the U. S. Public Health Service Hospital at Lexington, Kentucky on May 16, 1949. On seven previous admissions this patient had been diagnosed as having a character disorder with marked anxiety and dependent trends. He had used narcotic drugs for 21 years and had been denarcotized about 15 times, always relapsing to the use of drugs a few months following discharge. He originally began to use morphine to sober up from alcoholic sprees and, in 1930, had one attack of delirium tremens following a long alcoholic debauch. There was no familial history of epilepsy or insanity. On previous admissions the outstanding physical findings had been a chronic osteomyelitis of the left hip and pelvis. There was no history suggestive of syphilis and the Kahn reaction had been negative repeatedly.

On the day of admission the patient gave a history of using 5 to 6 grains of morphine intravenously daily for the past two years as well as 12 to 15 0.1 gram capsules of pentobarbital daily. He was confused, groggy and had dysarthria, ataxia and nystagmus. The pupils were constricted. Deep reflexes were normal. He was emaciated and weighed only 138 pounds, although he was 73 inches tall. Blood pressure was 100/64 mm. Hg. Numerous needle marks were seen over the antecubital veins. An old scar was noted on the left hip. The left leg was somewhat shortened and motion was limited in both the left hip and knee. The x-ray of the chest, urinalysis, blood count and blood serology revealed nothing of interest.

Following admission, patient was placed on 15 mg. of morphine, 10 mg. of methadone and 0.2 gram of pentobarbital four times daily. By the fourth day after admission his medication had been reduced to 5 mg. of methadone three times daily and 0.1 gram of pentobarbital twice daily. He became extremely nervous, apprehensive, developed a tremor and did not sleep. This dosage level was maintained during the fifth hospital day. Again he was quite restless, nervous and did not sleep. On the sixth hospital day he received 2.5 mg. of methadone at 6 a.m. and 0.1 gram of pentobarbital at 3 p.m. and at bedtime.

At 6:45 p.m. on the seventh hospital day, the patient began to threaten suicide. He said that he had a price on his head and that people were trying to poison him. He was transferred to the psychiatric service where a flow bath was administered. He was given 0.1 gram of pentobarbital at bedtime. On the following day the patient was seen in consultation. He was talking to non-existent people. When the consultant entered he begged the imaginary person's pardon, recognized the examiner and asked him to have a chair although there were no chairs in the room. He said that on the previous night some men, who were 9 feet tall, had come and taken him from the hospital to Cincinnati where "Dr. Ted Husing" forced him to drink a gallon of strychnine. He could not understand why he did not die as a result of taking the strychnine. He left Cincinnati and went back to his home in Georgia. He appeared to be having a variety of vivid visual hallucinations. He saw small people, colored children eating peanuts, and various animals. He was disoriented in time and place but not in person. Physical examination revealed a tall emaciated individual with limitation of motion of the left hip and knee joints. Marked fine tremor of hands, face and tongue was present. Blood pressure in the recumbent position was 120/78. On standing, it fell to 80/74. Pulse rate recumbent was 58 and on standing 106. The patient could stand for only a few minutes because of weakness. Otherwise, physical examination was not remarkable.

The patient was not given any further medication. Precautions were taken to prevent injury in the event of convulsions and his course was observed. He continued to have vivid visual hallucinations until the thirteenth hospital day. At this time he stated that he was still seeing things but he believed that they were imaginary and not real. By the twenty-first hospital day he appeared to be almost recovered, was no longer experiencing hallucinations, was oriented in time, place and person, and realized that his illness had been due to withdrawal of barbiturates. On the twenty-sixth hospital day he was discharged from the psychiatric service to one of the institution dormitories. He worked as a clerk in the library for the following three months and appeared to function as effectively as he had on previous admissions.

In subsequent interviews he stated that, even after he had been discharged to the dormitory, he still believed his hallucinations had been real. He thought that his sons had become addicted and had entered the same institution. He was afraid to ask anyone about this matter fearing that it might be true. He finally did inquire and, on being told that his sons were not in the institution, was greatly relieved. He remembered his hallucinations clearly and could describe them in detail two months after they had occurred. He stated that the experience was very similar to the attack of alcoholic delirium tremens which he had in 1930.

Comment: This case also represents an example of a man who, during excessively rapid withdrawal of barbiturates, had no convulsions but did develop a delirium. The striking resemblance of the condition to alcoholic delirium tremens is manifest.

Case 3. A male, aged 23 years, was admitted to the U. S. Veterans Administration Hospital at Lexington, Kentucky on November 11, 1949 in a comatose state and with a heavy odor of paraldehyde on his breath.

This patient was described by his father as having been a normal boy prior to entering the U. S. Marine Corps in 1945. After being inducted into the Marines, the patient did fairly well during his preliminary training but, before being sent to the Eastern Theatre of Operations, began to feel nervous and to have attacks of dyspnea and tachycardia on mild exertion. He boarded a transport with his unit but had to be taken off in Hawaii because of anxiety and cardiovascular symptoms. He was returned to the United States without having been in combat and was discharged in 1946 with a diagnosis of anxiety neurosis. While awaiting discharge from the Marine Corps, he began to drink excessively and, following discharge, continued to use alcohol in large amounts. He was admitted to the Nichols General Hospital at Louisville, Ky. on September 2, 1947 acutely intoxicated with alcohol. After regaining sobriety, he gave a history of periodic alcoholic debauches for 18 months. Following discharge against medical advice on September 23 he began to drink again and later was hospitalized in a private sanitarium where he received a series of 10 electroconvulsive treatments. He was also introduced to paraldehyde in this sanitarium. After leaving the sanitarium, he began to use pentobarbital in large amounts sometimes taking as many as 20 pentobarbital capsules and 6 to 8 teaspoons full of paraldehyde daily. In January, 1949, he attempted to discontinue pentobarbital but continued to take paraldehyde. He began to vomit, became delirious and was committed to the Nichols General Hospital. On admission, he was confused and disoriented. He denied the use of drugs. On the following day, he had a grand mal seizure and fell out of a chair striking his head on the floor. Electroencephalogram made one hour after the seizure showed predominant rhythm of 6 per second and a large number of high voltage 2 per second slow waves. This was interpreted as a post-seizure record. The following day the electroencephalogram was still slow but markedly improved. On January 14 the electroencephalogram was almost normal.

Despite this, the diagnosis of idiopathic epilepsy was made as well as a diagnosis of inadequate personality and addiction to alcohol, paraldehyde and barbiturates. The patient was discharged as improved on March 2, 1949. He immediately began to drink again and soon was taking a pint of whiskey, 20 pentobarbital capsules, and 6 teaspoons full of paraldehyde daily. He had a number of altercations with his father concerning his intoxication and finally made an abortive suicidal attempt, slashing his left wrist lightly. He was committed to the Nichols General Hospital on March 28, 1949 and, on admission, was boisterous, belligerent, uncoöperative, confused, fighting and begging for paraldehyde. On the third day following admission, he had two convulsions. Following these seizures, he was confused for a time but by April 2 appeared to be completely oriented in all spheres. On April 7, 1949, he was transferred to the U. S. Veterans Hospital at Lexington, Ky., where he remained under treatment until May 25, 1949. Following discharge, he began to take pentobarbital in large amounts, using these in conjunction with beer. He was committed to the Veterans Hospital at Lexington by his father on June 24, 1949 but on this occasion no symptoms occurred although withdrawal of barbiturates and other medication was abrupt. Following discharge, he immediately began to drink again and was soon using 1.0 to 2.0 grams of pentobarbital daily as well as an undetermined amount of paraldehyde. On November 17, 1949 he became angry because there was no paraldehyde in the house and assaulted his mother, striking her in the chest with a carving fork. A physician who was called gave him a large dose of paraldehyde and he was again committed to the Veterans Hospital at Lexington.

Seven hours after admission on November 17, 1949, the patient had recovered from the paraldehyde coma but was tremulous, nervous and begged for paraldehyde. No medication was allowed that night or the following morning. On November 18, the patient had a grand mal seizure and fell, striking his head and inflicting a laceration over his left eye. He was not given any medication although he vomited during the night and could not sleep. The following day he was confused, delirious, had hallucinations and was placed in wet packs. He became quite noisy, disturbed the ward at night and continued to be restless although 10 c.c. of paraldehyde were administered. Delirium and hyperactivity continued throughout November 21 and 22. Between 4 a.m. and 9 a.m. on November 23, he had five grand mal convulsions. The patient was given 0.5 gram of sodium amytal intravenously and a consultant called from the U. S. Public Health Service Hospital. A diagnosis of abstinence from hypnotics was made and restoration of barbiturate intake followed by gradual withdrawal was recommended. The patient was placed on 0.8 gram of pentobarbital daily and the dosage was reduced gradually over the course of the next eight days. The patient was rational by the next day and no further withdrawal phenomena were observed. Following recovery, psychiatric study revealed no evidence of major psychoses. There was no familial or personal history of epilepsy. An electroencephalogram made following recovery was essentially normal. Physical, psychometric and laboratory examinations were all essentially negative. Final diagnoses were inadequate personality, chronic alcoholism, addiction to pentobarbital and paraldehyde and convulsions and delirium due to abstinence from hypnotic drugs.

Comment: This case represents an example of mixed addiction to alcohol, barbiturates and paraldehyde occurring in an inadequate individual with anxiety and neurocirculatory asthenia. It is impossible to determine from the history whether the symptoms observed were due purely to abstinence from barbiturates or were due to abstinence from a combination of intoxicants. This case also illustrates the occurrence of barbiturate addiction in an individual who had never been addicted to opiates.

DIAGNOSIS

Barbiturate intoxication may be confused with alcoholism, bromide intoxication and with various neurological disorders. Frequently it is very difficult to determine whether the symptoms observed are due to alcohol or to barbiturates since both drugs are commonly used together. Barbiturate intoxication should be thought of in examining any individual who has signs compatible with alcoholic intoxication but who has no odor of alcohol on his breath or a negative blood test for alcohol. Patients often attempt to conceal their addiction so that the diagnosis may be dependent upon obtaining information from relatives or friends. The laboratory tests available for the detection of barbiturates in both blood and urine are difficult to carry out and are not generally available to most physicians. The characteristically fast electroencephalographic pattern is of great value in establishing the diagnosis. Organic nervous system disease can usually be excluded by the history, the absence of changes in the spinal fluid, the normal eyegrounds, normal skull x-rays, lack of sensory changes and by improvement in the symptoms following a *short* period of withdrawal. During abstinence, barbiturate addiction has to be differentiated from all conditions which produce major convulsive seizures and from the major psychoses. Ordinarily, the history and the subsequent course of the illness will suffice.

It is important to remember that acute barbiturate intoxication may be superimposed upon barbiturate addiction. After a patient who is acutely poisoned by barbiturates recovers from coma, one should immediately ascertain if he has been ingesting barbiturates chronically. If this is true, signs of abstinence are likely to appear unless treatment is instituted at once.

TREATMENT

Treatment of barbiturate addiction, like that of narcotic drug addiction, can be divided into two phases: withdrawal of drugs and subsequent rehabilitative and psychotherapeutic treatment. Abrupt withdrawal of barbiturates is absolutely contraindicated. Treatment must be carried out in a hospital. Once the diagnosis has been established, the patient should be given 0.2 to 0.4 gram (3 to 6 grains) of pentobarbital or an equivalent amount of any other barbiturate orally every six hours. The dosage should be adjusted to that amount which will just maintain a mild degree of intoxication continuously. After the patient has been observed for a day or two, reduction of the dosage of barbiturates can be started. Reduction must be carried out very slowly. The dosage should not be reduced more than 0.1 gram (1.5 grains) daily at any one time. Total withdrawal period should be extended over a period of two to four weeks. Occasionally it is wise to stop the reduction and to maintain the patient for several days on whatever dosage level has been reached. If the patient becomes nervous, apprehensive and weak, or if paroxysmal slow activity appears in the electroencephalogram, reduc-

tion should be stopped until these signs have cleared. If the diagnosis is made after convulsions or psychoses have appeared, the patient should immediately be given a large dose of some barbiturate—parenterally if necessary. After the symptoms have been controlled, a regular schedule of oral medication can be established and slow reduction begun as outlined above.

Patients undergoing withdrawal of barbiturates must be kept under close continuous observation. Their beds should be provided with sideboards so that if convulsions occur they will not fall to the floor. Patients should not attempt to walk, bathe or go to the bathroom unattended. Proper attention to fluid balance is essential and the diet should be light and soft throughout most of the period of withdrawal. Withdrawal of the opiate drugs can be carried on concomitantly with the withdrawal of barbiturates without increasing the danger of convulsions or psychoses appearing.

After withdrawal from barbiturates is accomplished, a long period of psychotherapeutic treatment designed to remove the fundamental cause of the addiction may be undertaken. Details of this phase of treatment are beyond the scope of this article.

PROGNOSIS

The prognosis of chronic barbiturate intoxication must always be guarded. The same tendency to relapse which is so characteristic of alcoholism and addiction to narcotics is present in addiction to barbiturates so that recurrence is very likely in a large proportion of patients.

DISCUSSION

It is obvious that barbiturates are addicting drugs. The same phenomena observed in addiction to narcotics—tolerance, emotional dependence and physical dependence are observed during the course of chronic barbiturate intoxication. In fact, addiction to barbiturates is far more serious than is morphine addiction. Addiction to morphine causes much less impairment of mental ability and emotional control and produces no motor incoördination. Furthermore, such impairment as does occur becomes less as tolerance to morphine develops and abstinence from morphine is much less dangerous than is abstinence from barbiturates.

The resemblance of the barbiturate abstinence syndrome to alcoholic delirium tremens is very striking. It has been commented on by many of the German authors^{17, 18, 19} and by Kalinowsky.¹³ In both conditions, weakness, tremors, insomnia, convulsions and a psychosis are frequently observed. In both disorders, the delirium is preceded by insomnia and tends to begin and to be worse at night. In both abstinence from barbiturates and in alcoholic delirium tremens, the hallucinations are predominantly visual and patients usually maintain orientation in person and become disoriented in time and place. Similar clinical pictures have been described following

withdrawal of chloral hydrate and paraldehyde from patients chronically intoxicated with these drugs.¹³ It appears that the syndrome known as delirium tremens is not caused solely by chronic alcoholic intoxication but represents a derangement which may follow chronic intoxication with a variety of hypnotic drugs of diverse chemical structure.

SUMMARY

1. Chronic intoxication with barbiturates is a true addiction. The same phenomena observed in addiction to narcotics are also present in chronic barbiturate intoxication—tolerance, emotional dependence and physical dependence.

2. The symptoms and signs of maintained chronic barbiturate intoxication include impairment of mental ability, confusion, regression, emotional instability, nystagmus, dysarthria, adiadokokinesis, tremor, hypotonia, ataxia in gait and station and depression of the superficial abdominal reflexes.

3. A characteristic train of symptoms follows abrupt withdrawal of barbiturates from chronically intoxicated persons. The barbiturate abstinence syndrome is characterized by diminution of signs of intoxication which is followed by weakness, tremor, insomnia, great anxiety, anorexia, nausea and vomiting, rapid weight loss, elevation of pulse and respiratory rates, increase in blood pressure, difficulty in making cardiovascular adjustments on standing, convulsions of grand mal type and the development of a psychosis. The delirium observed in the withdrawal of barbiturates resembles alcoholic delirium tremens and is characterized by anxiety, agitation, fever, insomnia, confusion, disorientation chiefly in place and time but not in person, delusions, and auditory and visual hallucinations.

4. Recovery from chronic barbiturate intoxication and the barbiturate abstinence syndrome is complete so far as can be determined by clinical means and by psychometric testing.

5. Abrupt withdrawal of barbiturates from addicted persons is contra-indicated. The only method of withdrawal which is known to be safe involves careful, slow reduction of the dosage of barbiturates.

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ABDOMINAL EPILEPSY VERSUS "ABDOMINAL MIGRAINE" *

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THE older clinical descriptions of the migraine syndrome have been little altered in this era in which interest has been centered on the basic neurophysiologic mechanisms involved in the migraine attack. It is still accepted that there exist clinical variants of common migraine or hemicrania, such as ophthalmic migraine, abdominal migraine, psychic equivalents of migraine, ophthalmoplegic migraine and facioplegic migraine. These variants remain to be explained. The old controversy as to the relation of migraine to epilepsy remains unsettled and the newer experimental work on migraine does not fully explain the different immediate mechanisms which must be operative to produce the distinctive clinical variants of the migraine syndrome.

It is the purpose of this paper to discuss one of these types and to indicate that the term "abdominal migraine" is inappropriate and pathophysiologically incorrect. The term has been used thus far because abdominal symptoms have occurred in a temporal relationship with the migraine syndrome, but it does not provide the correct implications with respect to the mechanism provoking the abdominal pain found in this disorder. I wish to suggest that the cases of "abdominal migraine" reported in the literature fall into two classes, (1) those which truly belong in the category of abdominal epilepsy, and (2) those which are abdominal epileptic manifestations occurring coincidentally with the migraine syndrome, or alternating with it. It will be shown that the abdominal symptoms occurring in the migraine syndrome are brought about by irritation of cortical areas 6, 5, and 3, and/or the diencephalon during the vasoconstrictor ischemic phase of the migraine episode, and that this in turn provokes abnormal intestinal motility, with resultant pain.

The clinical aspect of the syndrome of abdominal epilepsy¹ has as its main feature paroxysmal abdominal pain, which may appear as an isolated symptom. Among other symptoms which may be present in this syndrome are: an aura of "peculiar feelings," epigastric distress, nausea, at times vomiting, occasionally diarrhea, pallor, sweating, "rumbling sounds" in the abdomen, periodic attacks of abrupt behavior disturbances, nightmares, clonic movements of the abdominal muscles, rarely of the limbs without loss of consciousness, and post-ictal achiness, exhaustion, and sleep. It will be seen

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that these symptoms resemble closely and indeed almost in their entirety the manifestations which occur in many of the cases described in the literature as "abdominal migraine." In several earlier papers^{1, 2, 3, 4, 5} I have referred to experimental and clinical data indicating that a disturbed cerebral cortex in areas 6, 5, and 3 of Brodmann, and disturbance in the diencephalon, may provoke abnormal gastrointestinal activity, resulting in the pain of abdominal epilepsy. The experimental observations of Fulton and his co-workers,⁶ Spiegel, Weston and Oppenheimer,⁷ Penfield, et al.⁸ and Cushing⁹ have revealed that stimulation of areas 6, 5, and 3 of the cerebral cortex resulted in abnormal motility of portions or of the entire gastrointestinal tract with associated abdominal pain. Irritation of the diencephalon likewise resulted in disturbed gastrointestinal activity.

Brams¹⁰ in 1922 and Blitzsten and Brams¹¹ in 1926 reported a series of 32 cases of "abdominal migraine." They called attention to the scanty references to this disorder in the literature, and cited a number of authors¹² who had reported similar cases and who had made some notes regarding this condition. The term "abdominal migraine" was given because of the presence, or preponderance, of abdominal symptoms in association with a migraine episode. The abdominal symptoms referred to consisted of abdominal pain or, as they called it, "epigastralgia," nausea, vomiting, diarrhea or constipation. A personal or family history of migraine, allergic diathesis, convulsive disorders and the like was stressed as an important phase in establishing the diagnosis. Brams and Blitzsten divided their cases into three classifications: (1) those patients in whom periodic abdominal pain (epigastralgia) was an isolated symptom, or in whom the abdominal pain was associated with cephalalgic migraine; (2) a form in which typical migraine with accompanying cerebral manifestations was present, then terminated to be replaced by a seizure of abdominal pain with or without nausea and vomiting, and this at times again being replaced by cephalalgic migraine; (3) a larval type in which the abdominal pain may be mild or entirely absent, but wherein the nausea and vomiting and occasional diarrhea predominated. They stated: "The occurrence of the periodic attack of abdominal pain after the paroxysms of hemicrania were greatly diminished or disappeared completely, leads us to conclude that the abdominal pain may be regarded as a substitute for the attack of headache which was previously present in these cases."

Their explanation of the mechanism as to the cause of the abdominal pain, and the alternation of cephalalgic and abdominal symptoms, was vague and without substantiating evidence. For example, in the earlier paper of 1922, Brams¹⁰ stated: "There seems to be considerable doubt as to the seat of pain, but according to the most recent views, we are led to believe that the epigastralgia in these cases arises in the coeliac plexus and its branches." In the later paper¹¹ they stated: "It is possible, however, that the abdominal pain and other symptoms mentioned in our series of cases may be due to the

occurrence of a storm-center involving the region of the nuclei of the vagi, with transmission of the impulse to the sympathetic system." It is interesting that, in their recommended treatment consisting of ovarian extract, arsenic and "anti-migraine measures," they stated that the most favorable results were obtained by the use of tincture of cannabis (*cannabis indica* being listed pharmacologically as an anodyne, narcotic, and anti-spasmodic). Their case reports in which abdominal pain was the outstanding symptom were similar to those cases reported by me as abdominal epilepsy.

In my second paper on "Paroxysmal Abdominal Pain—A Form of Focal Symptomatic Abdominal Epilepsy,"⁸ I reported the case of a young man (Case 5) who presented a typical history of the migraine syndrome. He had periodic attacks of scintillating scotomas, severe headaches, and abdominal pain. He was treated for many years without relief despite the fact that anti-migrainous preparations, including ergotamine tartrate, were given. The attacks of abdominal pain lasted from several minutes to as much as two hours. Electroencephalographic studies revealed 5 to 7 per second waves of 10 to 30 microvolts in amplitude. Following hyperventilation, large, slow, 3 to 6 per second abnormal waves, varying from 50 to 100 microvolts, made their appearance. This patient was placed on a combination of diphenylhydantoin sodium, gm. 0.09 (1.5 grains), twice daily, and phenobarbital, mg. 16 (grain .25), three times daily, which resulted in complete freedom from the attacks of paroxysmal abdominal pain and his other symptoms. This case would, according to Brams and Blitzsten, fall into their group 2, and yet from electroencephalographic studies, and the response to anticonvulsant drugs, this patient had abdominal epilepsy. The cases reported by me, in which the isolated symptom of paroxysmal abdominal pain occurred, would have been placed by the above authors in their first group, but they represent cases of pure abdominal epilepsy. The type of cases considered in group 3 by Brams and Blitzsten as larval forms includes a large variety of cases with gastrointestinal symptoms, heretofore considered as vague, undiagnosable conditions, but which are in reality the representation of irritation of areas 6, 5, and 3, and/or the diencephalon, resulting in disordered gastrointestinal motility.^{1, 12}

The case described by Finney (1922)¹⁴ in which abdominal pain was the prominent feature and which was relieved only by the use of morphine, falls within the category of the condition known as abdominal epilepsy. Woltman¹⁵ reported three cases of abdominal crises which he believed to be "abdominal migraine." In his Case 7, he cited a woman of 46 years who presented this syndrome. Her brother had had abdominal crises of pain only, without vomiting or headache, ever since he was 18; another brother who had intense abdominal crises of pain and vomiting with headaches since the age of 18, and one of her sons had had abdominal crises of pain with or without vomiting, and always associated with headache. His Case 9, a 50 year old male, had had attacks of paroxysmal abdominal pain, occurring

about four times a year, since the age of 16. This patient also presented strong evidence of an allergic diathesis, as indicated by the occurrence of asthma and attacks of angioneurotic edema. Woltman also called attention to the fact that most of his patients, and those cited in the literature, have had at least one and at times many unrewarding abdominal operations, in an effort to disclose the cause of abdominal pain. The thread of allergic incidents can be seen woven in a large number of the cases of migraine and epilepsy; and allergy undoubtedly represents one of the exciting causes underlying these syndromes. These cases reported by Woltman compare in major respects with those reported by me as cases of abdominal epilepsy, even with respect to the history of one or more futile abdominal operations.

Buchanan¹⁶ cited seven cases of "abdominal migraine," two of which he reported. The first was that of a 13 year old male who experienced severe abdominal pain lasting from one-half to one hour. The abdominal pain was then followed by severe headache and vomiting. The entire episode lasted from one hour to a full day, and occurred once or twice a month. His second case was that of an eight year old boy with recurrent abdominal pain followed by scintillating scotomas and headache. The abdominal pain ceased with the onset of headache. It will be seen that the abdominal pain in his cases preceded the headache, indicating that the former evidently was provoked during the vasoconstrictor cerebral ischemic phase of the migraine episode. In the second case, the abdominal pain ceased with the second phase, that of vasodilatation, resulting in headache. Buchanan made the discouraging and enigmatic statement that "the condition is incurable and perfectly harmless except for its temporary inconvenience."

This disorder certainly is more than harmless and more than temporarily inconvenient, since by his own admission one patient had an unnecessary and fruitless appendectomy performed. Most of the patients suffering with this disorder have in the past been hospitalized numerous times, subjected to scores of examinations and varied forms of therapy without relief, and have had needless laparotomies done. Only too frequently they have been considered as psychoneurotics or malingerers.

Smith,¹⁷ in a paper concerning recurrent vomiting in children, observed that some of these children complained of headache and others of abdominal pain. He believed that this recurrent vomiting was a childhood equivalent of migraine, but noted that the attack could be aborted or terminated by the use of drugs such as bromides, amytal, luminal or codeine subcutaneously. This happy effect of anti-convulsant medication suggests that his patients had an epileptic equivalent rather than a migrainous one. The recent work of Klingman, Langford, Greeley and Hoefer,¹⁸ and of Lambert,¹⁹ shows that this type of abdominal paroxysmal pain and occasional vomiting encountered in children are of an epileptic order.

In a study of 104 patients having varied gastrointestinal symptoms, and in whom no underlying organic disease was demonstrable, Segal and Blair¹⁹

were able to classify these patients into six groups, among which was one called "paroxysmal abdominal pain" and another termed "migraine." The former group, consisting of 12 patients, was characterized by irregular attacks of sudden, severe abdominal pain. This group, according to the authors, falls directly into the category of abdominal epilepsy. They noted that eight, or 67 per cent, of these patients had abnormal electroencephalograms and, further, that these patients responded well to the use of anti-convulsant drugs such as dilantin sodium and the barbiturates. Of the 10 patients who constituted the migraine group, the authors said: "This syndrome contained those people in whom the abdominal symptoms were considered as migraine equivalents, because they occurred in patients with the type of headache associated with migraine." Not only did all 10 of these individuals have abnormal electroencephalograms, but six of the seven patients who had been given dilantin sodium showed improvement. The two latter observations would tend to eliminate this "migraine" group from a true migraine representation and to place the cases in the category of abdominal epilepsy. Segal and Blair made no reference to the effect of ergotamine tartrate upon the abdominal pain occurring in their "migraine" patients. The response of this group to anti-convulsant therapy, and the appearance of abnormal electroencephalographic tracings in all of them, are good evidence as to the epileptic nature of the paroxysmal abdominal pain.

As far back as 1873, Liveing,²⁰ in an extensive study on migraine, considered the latter to be related to epilepsy. He, like many others, held the belief that migraine might pass over into epilepsy and vice versa. Flatau,²¹ in his study of 500 cases of migraine, noted that 36 of this group developed convulsive seizures. Riley²² stated: "By many writers, migraine is considered to be a form of convulsive state. Migraine may disappear and give place to convulsive seizures at any time in a patient's life, or the reverse may occur. The two disorders may co-exist, and cause much uncertainty in the effort to ascribe the symptoms to the proper disorder." Bassoe²³ observed that statistical analysis of the relation of migraine to epilepsy reveals that there is only a small percentage of cases of epilepsy in the ancestors of migraine patients, but a large proportion of migraine in the ancestors of epileptic patients. In these cases, the hemicrania originated early in life and the epileptic manifestations occurred much later. Phillips,²⁴ in discussing the relation between migraine and epilepsy, also noted the late occurrence of convulsions in individuals having migraine, and he felt these to be due to cardiovascular changes. His observations have been concurred in by Bassoe. It is extremely interesting that Bassoe,²³ in commenting on the subject of "abdominal migraine," said: "Like convulsions, so paroxysms of abdominal pain may be substituted for those of headache."

Wilson,²⁵ in discussing "abdominal migraine," said: "At times too, cerebral and abdominal syndromes alternate, while larval types without pain, but with nausea, vomiting and diarrhea, have been reported. Should ab-

dominal symptoms occur alone, without a history of any cerebral migraine, their diagnosis as a possible variant is naturally difficult, and may be wrong. Some of these alleged visceral equivalents might be epileptic, and not migrainous. . . ."

There is abundant evidence in the literature that the "white," or angiospastic, phase of migraine does produce cortical ischemia, resulting in many of the following symptoms which may be encountered in the migraine syndrome: localized twitchings, fascicular or myoclonic contractions, monoplegia, hemiplegia, paresthesias, scotomas, hemianopsia, vertigo, mental dullness, euphoria and other psychic phenomena, irritability, amnesia, dizziness, and incoördination. That involvement of subcortical gray matter also occurs may be adduced by the fact that vegetative phenomena appear in the migraine syndrome. Nielsen and Ingham²⁶ cited five cases of the migraine syndrome in which there was evidence of focal vascular disturbance with resultant involvement of the cerebral cortex and subcortical ganglia producing such manifestations as disorientation in space, clouding of consciousness, emotional imbalance, staggering gait and lapses of memory.

Lashley,²⁷ in discussing the scotomas of migraine, said: "Such phenomena can be made intelligible by the assumption that the integrative mechanism of the striate cortex tends to reproduce a pattern of excitations aroused in one region. . . . Such a reduplication of patterns should result from the spreading of waves of excitation from points of initial stimulation, by analogy with the transmission of wave patterns on the surface of a liquid. Recent work on the histology of the cortex reveals an anatomic basis for radiation of such waves."

Further evidence that the scotomas of migraine represent discharges from cortical gray matter secondary to the vasoconstriction of cerebral vessels is to be found in the work of Romano, Engel, et al.²⁸ Romano, Engel and their co-workers, in describing a "migraine-like syndrome complicating decompression sickness," observed that scintillating scotomas and blurring of vision, usually followed by headache, were occasional symptoms among subjects experiencing decompression sickness during exposure to simulated high altitudes. Other focal neurological signs such as hemiparesis, sensory disturbances, and aphasia were encountered at rare intervals. They believed this syndrome to bear a striking resemblance to clinical migraine, and noted that the reaction tended to occur repeatedly in certain individuals and not at all in others. The scotomas, and the associated symptoms seen in some of the patients, such as nausea, vomiting, abdominal pain and diarrhea, resembled in every way the symptoms experienced in true migraine. One of their subjects developed a convulsion, followed by right hemiparesis, during one of these migraine-like episodes. Of the 155 subjects in this experiment, 17 experienced the reaction of the migraine-like disturbance a total of 46 times. The authors concluded that the neurological disturbances have their origin in the cerebral cortex and result from angiospasm. This was based upon the following characteristics: (1) unilateral distribu-

tion, (2) homonomous visual field defects with sparing of central vision, (3) migration of scotoma toward the periphery, (4) absence of retinal changes, (5) the salutary effect of vasodilators on the scotomas but not the headache, and (6) focal electroencephalographic changes. The headache in this condition resembles migraine in the following ways: (1) the clinical description, (2) associated phenomena such as nausea and vomiting, (3) location contralateral to the neurological signs, (4) onset after scotoma, and (5) absence of electroencephalographic changes during the headache. Electroencephalographic recordings revealed irregular 4 to 7 per second waves from the occipital region contralateral to the visual field defect during the scotoma phase of the migraine syndrome. They interpreted this syndrome as representing a vasospastic complication of decompression sickness, and left as open questions whether the vasospasm is brought on reflexly or humorally, from distant or from neighboring areas of tissue damage due to tissue bubbles.

The important experiment of Arvanitaki²⁹ explains much regarding the spread of scotoma activity in migraine and the underlying principle of Jacksonian epilepsy and other forms of focal symptomatic epilepsy. Arvanitaki's preparation of single complete neurons and his study of the rhythmic activity which develops in the isolated neuron are important evidence with respect to the spread of nervous impulses from ganglion cells. He demonstrated that if an isolated nerve cell showing rhythmic activity is brought close to an inactive nerve cell, the latter will often begin to beat in phase with the former, and if two active nerve cells are placed in proximity to each other, their activity may become synchronous, and when they are separated they return to an independent rhythm.

If the concept of J. Hughlings Jackson³⁰ is accepted (and there are increasing data which now establish his view) that "epilepsy is a name for occasional, sudden, excessive, rapid and local discharge of gray matter"—then the ganglion cell "irritation" consequent to the ischemia of vasoconstriction occurring in migraine results in abnormal discharges which are of the nature of an epileptic dysrhythmia. Putnam and Hoefer³¹ have demonstrated electroencephalographically that abnormal cerebral discharges are provoked in those conditions in which cerebral anoxia occurs. Gibbs, Davis and Lennox³² also showed the effect of anoxia upon the cortical gray matter, and they said: "Nitrogen breathing, standing with a lowered blood pressure and over-ventilation, all of which produce large, slow waves in normal subjects, also tend to precipitate seizures in epileptic persons."

Strauss and Selinsky,³³ in a study of 20 patients with the migraine syndrome, showed abnormal electroencephalographic findings in nine. Five of these nine patients showed, in the electroencephalogram, bursts of three and six per second waves after hyperventilation. These abnormal potentials could not be obtained in the headache-free intervals, or after ergotamine tartrate had dispelled the headache. However, when the headache persisted after the injection of ergotamine, the record continued to be abnormal.

Headaches induced by histamine did not reveal abnormal potentials in the electroencephalogram. This difference between histamine headaches and spontaneous paroxysmal headaches confirms their view that these two types of headaches have dissimilar mechanisms. This work again indicates that the electroencephalographic abnormalities in migraine patients occur during the vasospastic phase, and the effects of the latter may persist in the cerebral cortex for a time even after the headache has made its appearance. Thus the tissue hypoxia resulting from the vasoconstrictor ischemic phase of migraine establishes the conditions necessary to evoke abnormal discharges (perceived in the electroencephalogram) resulting in the cerebral manifestations of this syndrome.

Since, in migraine, vasoconstriction involves the striate cortex producing scotomas, the sensory cortex producing somatosensory phenomena, the motor strip producing muscular twitchings and myoclonic contractions, and the frontal lobes and thalamus with psychic phenomena and disturbed consciousness, then it is not at all unlikely that the same process can and does occur in areas 6, 5, and 3, and/or the diencephalon, to produce abnormal gastrointestinal motility and resultant abdominal pain.

If one accepts the generally conceded view that the cephalalgic pain of migraine is of vascular origin, then one must show that the abdominal pain in "abdominal migraine" likewise is of local vascular origin. Nothing has appeared thus far in the literature to indicate that this is so. True migraine is initiated with vasoconstriction, and the resulting involvement of cerebral vessels results in ischemia, which brings about the early symptoms of the syndrome, such as scotomas, etc. The proof that the first phase is due to vasoconstriction is established by the fact that vasodilator drugs afford relief in this stage, provided these agents are given in the dosage which causes an increase of circulation through the brain without a marked fall in blood pressure.²⁸ The work of Wolff and his co-workers³⁴ shows very conclusively that the pain in the second phase of the migraine syndrome is due to vasodilatation with stretch of pain fibers in the large vessels of the scalp and in some intracranial vessels. The clinical and experimental data regarding the mechanism of the migraine headache need not be reviewed at this point, nor the differential points between the migraine headache and that induced by histamine.

In none of the communications in the literature has there been any evidence that the abdominal pain of abdominal migraine is of vascular origin, as has been established in true cephalalgic migraine. The pain occurring in so-called "abdominal migraine" has, up to the present been attributed to such factors as "a storm arising in the vagal nuclei,"¹¹ "coeliac neuralgia,"¹⁰ or "sympathetic neuralgia."³⁵ Groh and Veal³⁵ reported a case of cranial and "abdominal migraine" in which a lumbar sympathectomy was performed, with complete relief of abdominal pain. On the basis of this, they concluded that "abdominal migraine represents a form of sympathetic neuralgia located in the lower portion of the sympathetic chain." They were unable,

however, to show that the abdominal pain was due to the stretch of pain fibers in dilated intra-abdominal blood vessels. The disappearance of pain in this case was due to the fact that the proximal arc of the afferent pathway for pain was interrupted, but the underlying mechanism initiating the pain was not affected.

The accompanying or associated appearance of nausea, vomiting and diarrhea in "abdominal migraine" strongly suggests disturbed motility of

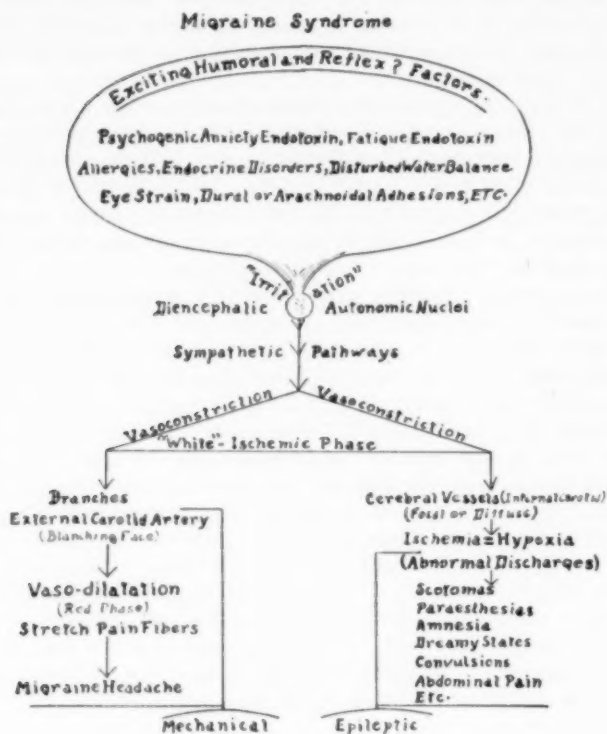


FIG. 1.

the bowel, and therefore the mechanism in the production of pain is quite different from the known vascular origin of pain in cephalgic migraine. The pain in abdominal epilepsy, and in "abdominal migraine," is due to the irritation of the pain-sensitive nerve endings in the wall of the intestinal tract which have been provoked into abnormal motility by discharges arising in premotor area 6, and post-Rolandic areas 5 and 3, and/or the diencephalon. In cephalgic migraine, or hemicrania, the pain is due to the

dilatation of blood vessels with consequent stretch of the mural pain-sensitive fibers. This impulse is transmitted by the afferent sensory system ultimately to the cerebral sensory cortex. No comparable vascular mechanism has been demonstrated as yet in so-called "abdominal migraine."

The exciting factors to which the migraine syndrome has been attributed are numerous. Among these are such causes as allergic reactions, endocrine dysfunction, disturbed fluid balance of the body, changes in blood volume with hemoconcentration, toxic metabolites, psychogenic causes, fatigue, and tissue bubbles in the brain occurring in decompression sickness. Any one or more of these factors may produce an irritation of unstable or morphologically or biochemically disturbed autonomic nuclei in the diencephalon, with resultant discharge of abnormal impulses over the autonomic fibers subserving control of the blood vessels of the scalp, dura and cerebral vessels. The first impact of this stimulus results in vasoconstriction, or the white phase, which provokes the abnormal responses referred to before, and with the termination of this abnormal impulse there is secondary vasodilatation resulting in the red phase, and, coincidentally, stretch of pain fibers in the pain-sensitive vessels of the scalp, dura and pia. It is during the latter phase that the cephalalgic pain of migraine occurs. It is during the white, or vasoconstrictor, phase that the phenomenon of abdominal epilepsy or of so-called "abdominal migraine" occurs. In the diagrammatic representation of the mechanism of the migraine syndrome (figure 1), it will be seen that the cerebral phase has been designated as being of an epileptic order.

DISCUSSION

The question will arise as to the importance of changing the term "abdominal migraine" to that of "abdominal epilepsy." I feel that this is not merely a question of nomenclature, but one of applying the inherent value of semantics and the correct interpretation of the underlying mechanism of this disorder. Moreover, the pragmatic aspect of treatment is dependent upon this correct interpretation. If the conception of paroxysmal abdominal pain in its isolated form or, the form exhibited as an accompaniment to the migraine syndrome, is interpreted in the mechanical vascular connotations of migraine, then the use of anti-migrainous drugs will afford no relief, since the latter affect dilated blood vessels. If, on the other hand, the view is adopted that paroxysmal abdominal pain is an epileptic display in the migraine syndrome resulting from abnormal discharges emanating from certain ganglion cells "irritated" by the hypoxia of the ischemic vasoconstrictor phase of the syndrome, then adequate and effective treatment can be given for this symptom. This treatment consists of anti-convulsant drugs and measures, as outlined in previous papers.^{1, 2, 3, 4, 5} Not only can the symptom of paroxysmal abdominal pain be relieved and prevented, but the excessive, time-consuming, annoying and expensive studies to which these patients have been subjected can be avoided.

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A CLINICOPATHOLOGIC STUDY OF BRONCHIAL ASTHMA WITH CONSIDERATION OF ITS RELATIONSHIP TO THE "GENERAL ADAPTATION SYNDROME" *

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INTRODUCTION

BRONCHIAL asthma has been a subject of controversy among clinicians and pathologists since the recognition of this disease. Salter,¹ almost a century ago, stated that "... asthma is a disease about whose pathology more various and discrepitant ideas prevail than about any other disease that could be named. . . ." The first major study of the pathology of this disease by Huber and Koessler² in 1922 has been followed by many individual case reports. This literature has recently been reviewed by Rackemann,³ Unger⁴ and Gay.⁵ Because of the persistence of varied opinions concerning bronchial asthma, and also because of the scarcity of reports dealing with large groups of fatal cases, a clinicopathologic study of fatal bronchial asthma was undertaken.

MATERIALS AND METHODS

Selection of cases has always been difficult in a discussion of bronchial asthma. Distinctive clinical or pathologic features may be lacking in any individual case. All cases from the period of January 1, 1934 through April 1, 1948 listed in the files of the Mallory Institute of Pathology of the Boston City Hospital as "history of bronchial asthma" or "findings consistent with bronchial asthma" were reviewed. There were 61 such cases. The clinical record, pathologic protocol and all available microscopic sections of each were examined. Of these 61 cases, only those with either a typical history of bronchial asthma or tissue changes considered diagnostic of this disease^{2, 6, 7, 8, 9} were accepted for final analysis. A total of 46 cases was finally selected as valid material for this report.

RESULTS

For purposes of analysis, the 46 cases have been divided into three groups: (I) those patients whose death occurred during an attack of bronchial asthma; (II) those patients who died because of diseases which fre-

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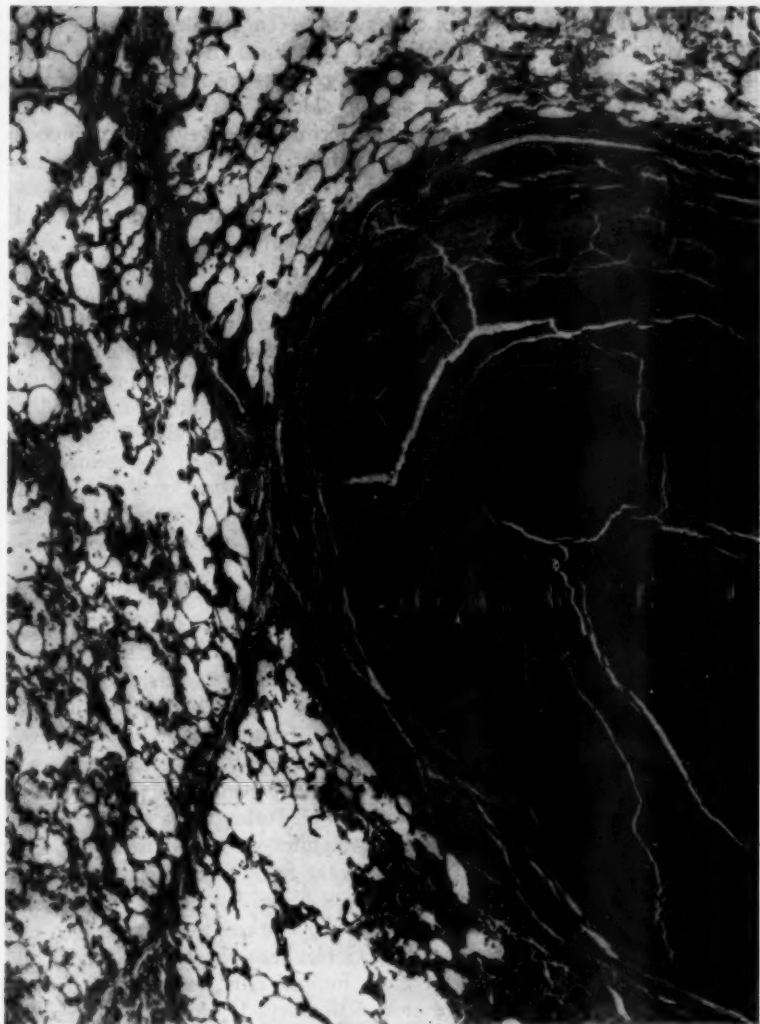


FIG. 1. Bronchus $\times 50$. (Phloxine methylene blue.) Case 2, table 1. A medium-sized bronchus containing a mucous plug. Sacculations of the epithelium are present. Bronchus surrounded by emphysematous lung.

quently accompany and may be related to bronchial asthma; and (III) those patients who died because of intercurrent disease.

Group I (table 1): Of the 46 patients, 13 died during an attack of bronchial asthma. These patients, six males and seven females, ranged from six to 80 years of age. The duration of symptoms of bronchial asthma varied from one month to 15 years. Of six patients with a duration of one year or less, five were 49 years of age or older. Four patients had had bronchial asthma for 10 to 15 years and terminally developed continuous asthma not responsive to therapy. One patient, whose pulse and respirations ceased during an attack, developed a left pneumothorax and a subcutaneous and mediastinal emphysema following intracardiac adrenalin and artificial respiration. Evidence of extrinsic allergy was definite in only one patient and uncertain in a second patient. In three patients, the bronchial asthma appeared to be associated with sinusitis. Blood eosinophilia was present in five patients and absent in four; data were not available in four others. Five patients were clinically considered to have either decompensated arteriosclerotic heart disease or bronchial asthma with acute heart failure; three of these patients received at least 15 mg. of morphine sulfate in the 24 hours preceding death. One patient had signs and symptoms of decompensated cor pulmonale for one year as well as repeated attacks of bronchial asthma. Two patients terminally developed peripheral vascular collapse. An incorrect diagnosis of coronary thrombosis was made clinically in one of these patients. The family histories were non-contributory.

The majority of the pathological findings of these 13 cases were those which have been described as typical of an attack of bronchial asthma.^{2, 6, 7, 8, 9} Emphysema of moderate to marked degree was present in all cases. However, areas of atelectasis alternating with areas of emphysema were noted only in the six year old boy. Mucous plugs, especially marked in the medium-sized bronchi, were seen in all cases (figure 1). Curschmann's spirals were seen in six cases. Desquamated epithelial cells, scattered eosinophiles and neutrophiles were prominent in the mucus. Eosinophiles, both in the lumen and the wall, were noted in all but one case of this group (Case 10, table 1). Large groups of neutrophiles were seen focally in the lumen and wall in several cases. Folding of the epithelium was a prominent feature in seven out of 13 cases; it was absent in only one case. However, desquamation of epithelium was frequently so marked that the degree of folding could not be ascertained clearly. Goblet cells appeared distended in 10 cases. The state of the cilia of the columnar cells was difficult to determine. Where these cells were not desquamated, cilia were present. Atrophy of the epithelium was not seen. There was squamous metaplasia in one case. Mucous glands were active and occasionally were surrounded by groups of neutrophiles. The basement membrane was thickened and hyalinized in the medium and large-sized bronchi in all cases (figure 2).

TABLE I

Case No.	Sex	Age at Death	Duration of B.A.	Present Illness	Eos.	Clinical Diagnosis	Anatomical Diagnosis
1	F	64	4 mos.	Frequent attacks of dyspnea. Entered in expiratory distress, in extremis. Treated as cardiac with repeated doses of morphine and atropine.	—	Arteriosclerotic heart disease. Cardiac asthma.	Bronchial asthma.
2	F	18	8 mos.	Bronchial asthma in infancy and in year of death. Chronic severe asthma 8 months. Continuous last 24 days. Sinusitis.	18%	Acute cardiac failure. Bronchial asthma.	Bronchial asthma.
3	M	49	1 yr.	Medicolegal. Severe attack of bronchial asthma at home. Dead on arrival at hospital.	—	Bronchial asthma.	Bronchial asthma. Rheumatic valvulitis, healed, mitral and aortic valves.
4	M	6	4 yrs.	Medicolegal. Eczema for years with "multiple extrinsic allergies." Bronchial asthma for 4 yrs. Continuous last 5 days. Dead on arrival.	—	Bronchial asthma. Bronchitis.	Bronchial asthma. Cerebral edema.
5	F	80	71 yr.	Productive cough and dyspnea 1 yr. with frequent asthmatic attacks for 2 months. "Music-box chest." Treated as cardiac. Multiple doses of morphine terminally.	4%	Bronchiectasis. Bronchial asthma. Bronchopneumonia. Arteriosclerotic heart disease.	Bronchial asthma. Cor pulmonale.
6	M	60	15 yrs.	In status asthmaticus on admission. Relieved by treatment. Sudden dyspnea and death on third day.	0	Bronchial asthma. Status asthmaticus. ? Coronary thrombosis. ? Rt.-sided heart failure. Embryosoma.	Bronchial asthma. Cor pulmonale. Central hemorrhagic necrosis of liver.
7	F	64	10 yrs.	Chronic bronchial asthma. Morphine sulfate gr. $\frac{1}{2}$ on admission. Died in sleep.	—	Acute heart failure. Bronchial asthma.	Bronchial asthma.
8	M	56	11 yrs.	First attack followed operation for sinusitis. Intermit- tent since. Continuous last three weeks. Adrenaline- fast. Died in peripheral collapse.	2%	Bronchial asthma.	Bronchial asthma.
9	F	44	8 yrs.	Chronic bronchial asthma. Dyspnea, orthopnea, ankle edema 1 yr. Entered with attack of bronchial asthma and signs of right failure. E.K.G.: R.A.D. Died four- teenth day.	0	Periculous anemia, treated. Bron- chial asthma. Asthmatic bronchi- tia. Cor pulmonale.	Bronchial asthma. Cor pulmonale. Cardiac failure, right.
10	F	63	15 yrs.	Intermittent bronchial asthma. Continuous for last month. Reinstated all therapy.	5%	Bronchial asthma. Status asth- maticus. Arteriosclerotic heart dis- ease decompensated.	Bronchial asthma.
11	M	63	10 mos.	Severe intermittent wheezing 10 mos. Emphysema. Hy- pertension (B.P. 215/120). Increasing, varying auto- temia. Died in sudden dyspnea.	15%	Chronic bronchial asthma. Em- physema. Chronic pyelonephritis. Sinusitis.	Bronchial asthma. Chronic pyelo- nephritis. Benign nephrosclerosis. Hypertensive arteriosclerotic heart disease. Cardiac failure.
12	F	58	1 month	Acquired dog 6 months before death. Hacking morning cough 4 months. Intermittent asthma 1 month. En- tered in peripheral collapse and acute dyspnea. Died first day.	0	Bronchial asthma. Status asth- maticus.	Bronchial asthma. Cor pulmonale (autopay restricted to chest).
13	M	46	12 yrs.	Severe intermittent bronchial asthma, worse last year. Reinstated in hospital. Treated with morphine, atropine, adrenaline and artificial respiration was followed by ap- pearance of left pneumothorax and subcutaneous emphy- sema and death.	10%	Bronchial asthma. Status asth- maticus. Pericarditis. ? induced, ? spontaneous. Subcutane- ous and mediastinal emphysema.	Bronchial asthma. Left pneumo- thorax. ? induced, ? spontaneous. Subcutaneous and mediastinal em- physema.



FIG. 2. Bronchus $\times 100$. (Phloxine methylene blue.) Case 4, table 1. A medium-sized bronchus showing many distended goblet cells, folding of the epithelium, thickening and hyalinization of the basement membrane, infiltration of lymphocytes, plasma cells and scattered eosinophiles in the lamina propria, active mucous glands and a prominent muscular layer.

Within the walls of the bronchi, lymphocytes and plasma cells were abundant. These cells were not found in the muscular layer, but were present in the lamina propria and external to the muscular layer. In several cases, the number of plasma cells was greater than that of the lymphocytes. The thickness of the muscular layers of the small bronchi was variable, but generally did not appear greater than normal. The muscle layers of the medium and large bronchi were prominent but were not definitely thickened. Sacculations of the bronchial wall were present in 11 cases. Congestion and edema of the walls were moderate. No remarkable changes in the cartilage of the bronchi were seen. The walls of the respiratory bronchioles were uniformly very prominent. A small patch of bronchopneumonia was present in one case (Case 9, table 1). Except for microscopic emphysema, the lungs showed no other changes.

The heart weights of the adult patients varied from 220 to 460 gm. and averaged 341 gm. (average normal 300 gm.). The right ventricle measured 5 mm. or more in thickness in four patients in the absence of hypertensive or valvular disease (average normal 2 to 4 mm.). Microscopically, focal areas of fibrosis were seen in three cases in association with moderate coronary atherosclerosis. In one case, scattered eosinophiles were seen in the interstitial tissue of the myocardium (Case 2, table 1). The liver showed congestion and atrophy in four cases (Cases 3, 7, 11, and 13, table 1), and central hemorrhagic necrosis in one case (Case 6, table 1). Gross examination of the lymph nodes was not remarkable. Mediastinal lymph nodes of eight cases were available for microscopic examination. In each lymph node examined, the essential architecture was intact but germinal centers were prominent and showed varying but usually marked degrees of pyknosis and karyorrhexis of lymphocytes and cytophagocytosis of nuclear debris by macrophages. Anthracotic pigment was present in six cases but was located in the germinal centers in only one. Eosinophiles were seen in the lymph sinuses of two patients. The thymus was available in one case and showed areas of marked pyknosis and karyorrhexis of thymocytes and phagocytosis by macrophages (Case 2, table 1). The spleens were not grossly remarkable in appearance or weight (averaging 149 gm.), but microscopically, four of the 10 cases examined had changes in Malpighian corpuscles similar to but less marked than those previously described in the lymph nodes and thymus. Eosinophiles were seen in the sinuses of a few. The adrenal glands were not remarkable grossly; weights were not available. Phloxine methylene blue stains and/or Sudan IV stains of the adrenals of nine cases were examined. Two showed marked patchy depletion of lipid (Cases 9 and 10, table 1), and four showed slight patchy depletion. Three adrenals were filled with lipid material. In figure 3 photomicrographs of the thymus, mediastinal lymph node, spleen, and adrenal cortex of Case 2, table 1, are presented. Figure 4 illustrates the lymphoid and adrenal findings in Case 1, table 1. The bone marrow was

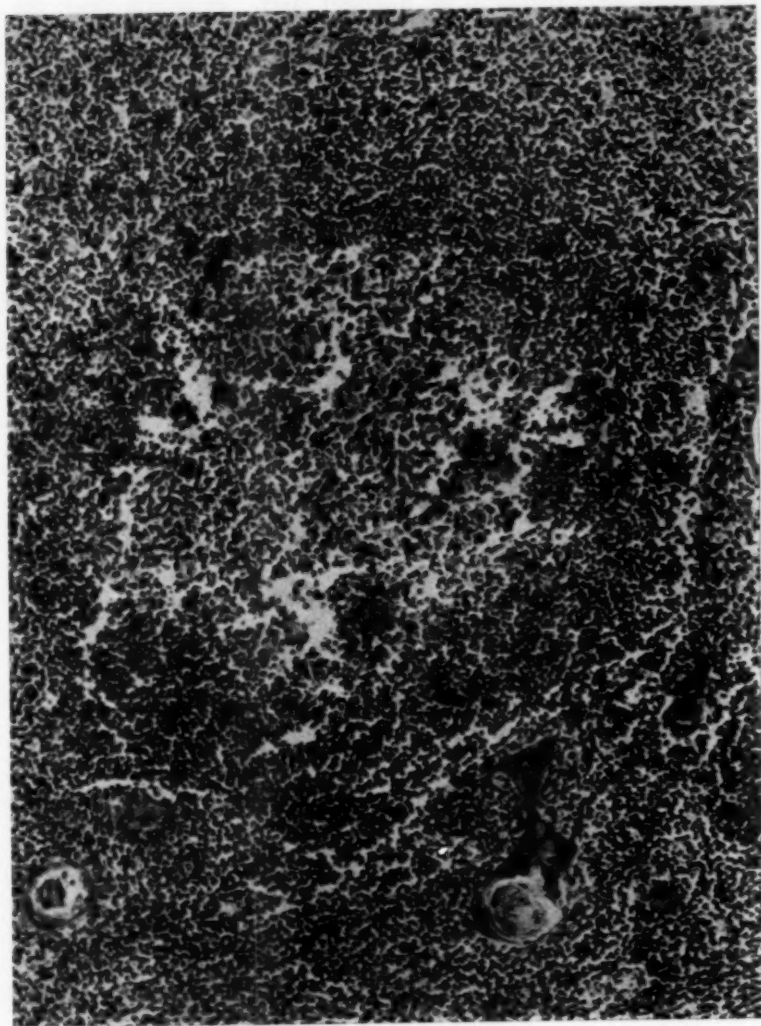


Fig. 3A. Thymus $\times 200$. (Phloxine methylene blue.) Case 2, table 1. Germinal center with marked pyknosis and karyorrhexis of thymocytes and cytophagocytosis of nuclear debris by macrophages.

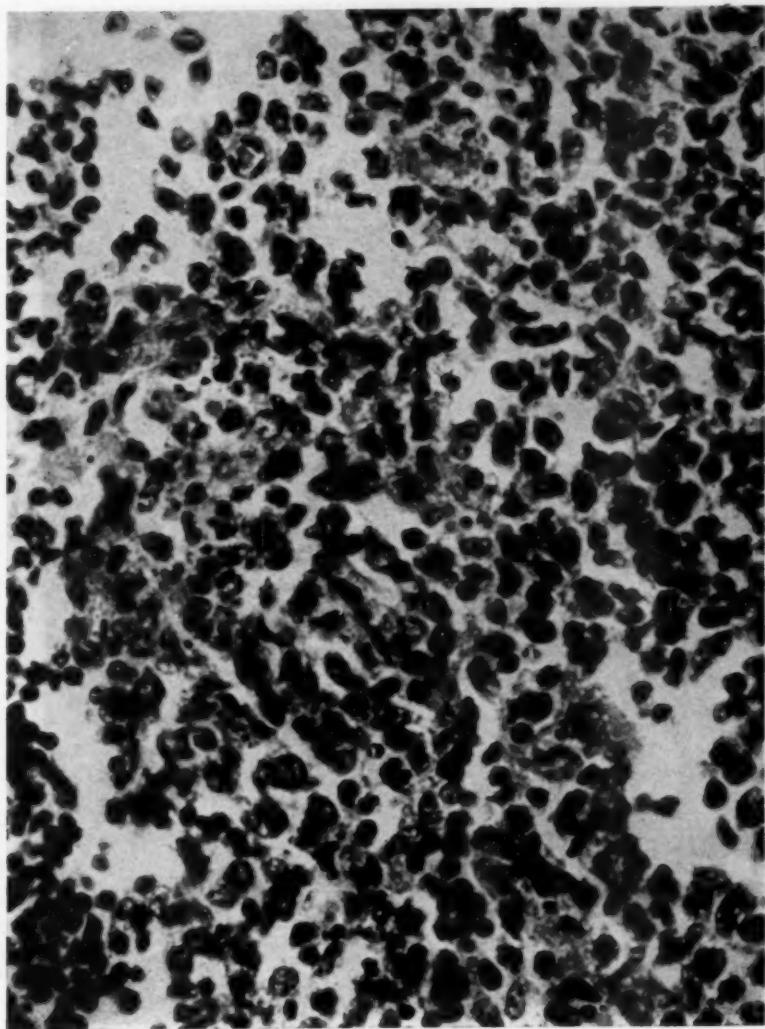


FIG. 3B. Thymus $\times 800$ illustrating greater detail of field shown in figure 3A.

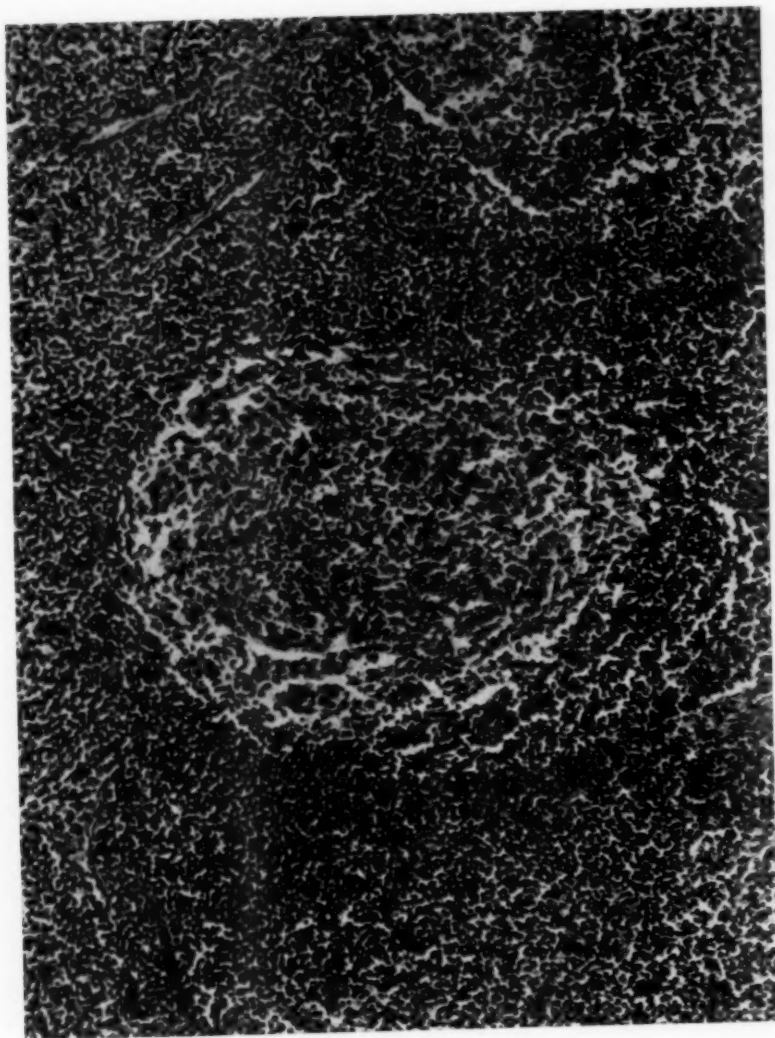


FIG. 3C. Mediastinal lymph node $\times 200$. (Phloxine methylene blue.) Case 2, table 1. Large cellular germinal center with moderate pyknosis, karyorrhexis of lymphocytes and phagocytosis of nuclear debris by macrophages.

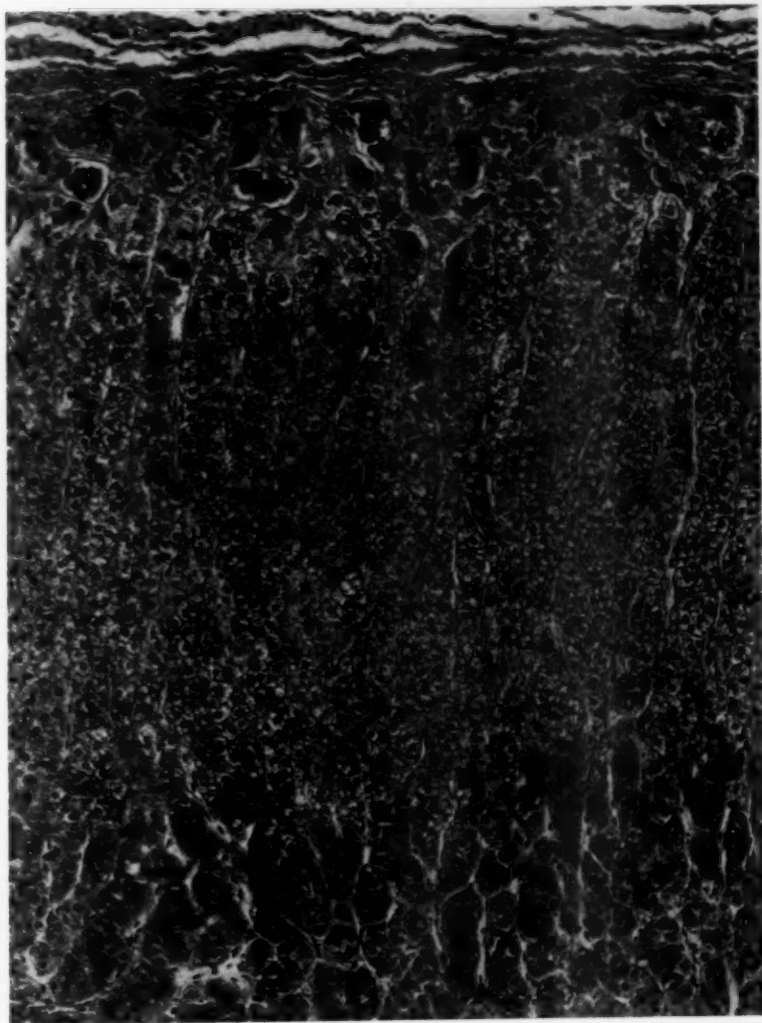


FIG. 3D. Adrenal cortex $\times 200$. (Phloxine methylene blue.) Case 2, table 1. Zona fasciculata is well filled with lipid; zona reticularis is thick.

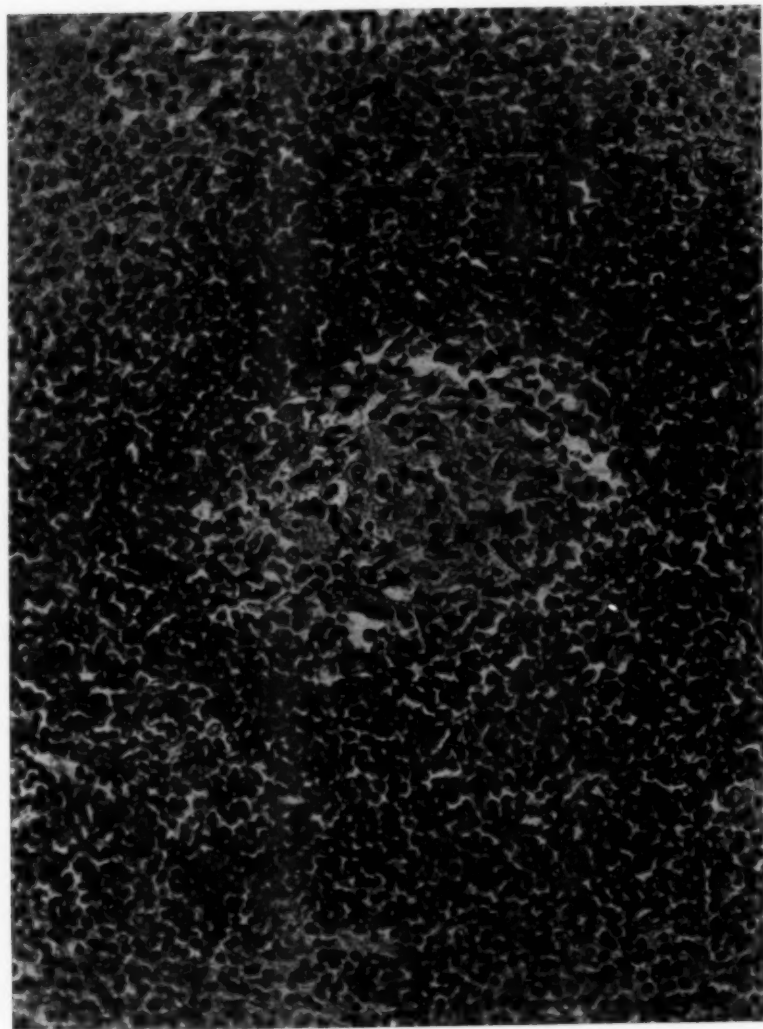


FIG. 3E. Spleen $\times 400$. (Phloxine methylene blue.) Case 2, table 1. Malpighian corpuscle with changes similar to those seen in lymph node illustrated in figure 3C.

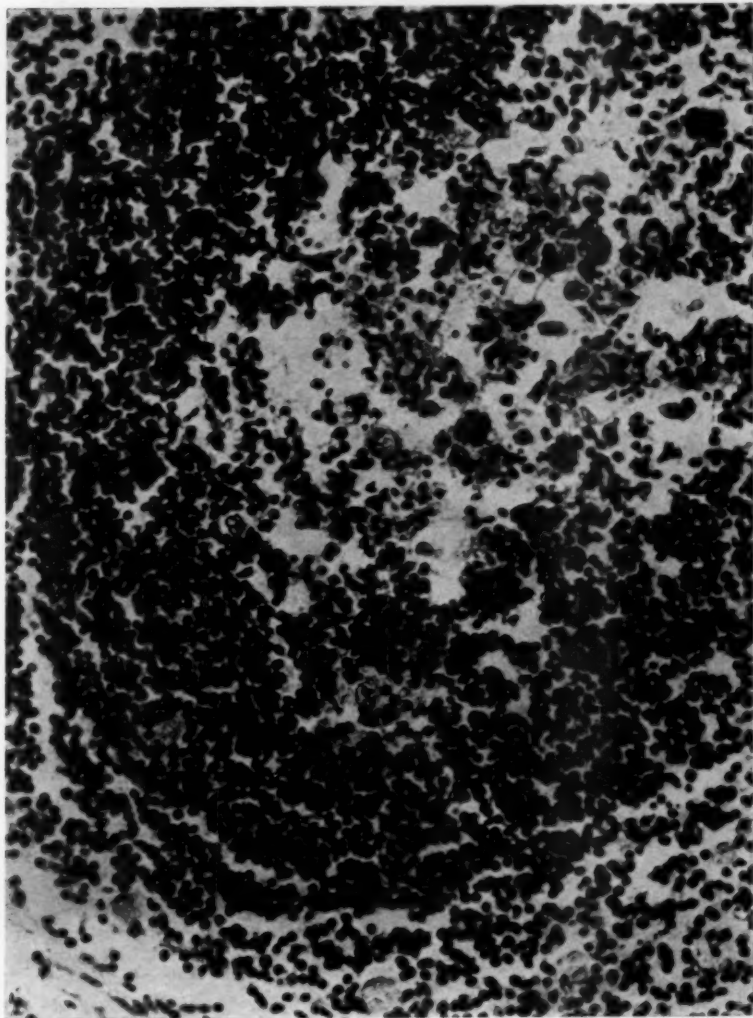


FIG. 4A. Mediastinal lymph node $\times 400$. (Phloxine methylene blue.) Case 1, table 1. Germinal center with edema, macrophages with cytophagocytosis and karyorrhexis and pyknosis of lymphocytes.



FIG. 4B. Spleen $\times 400$. (Phloxine methylene blue.) Case 1, table 1. Germinal center largely composed of lymphoblasts and macrophages with a few pyknotic cells.

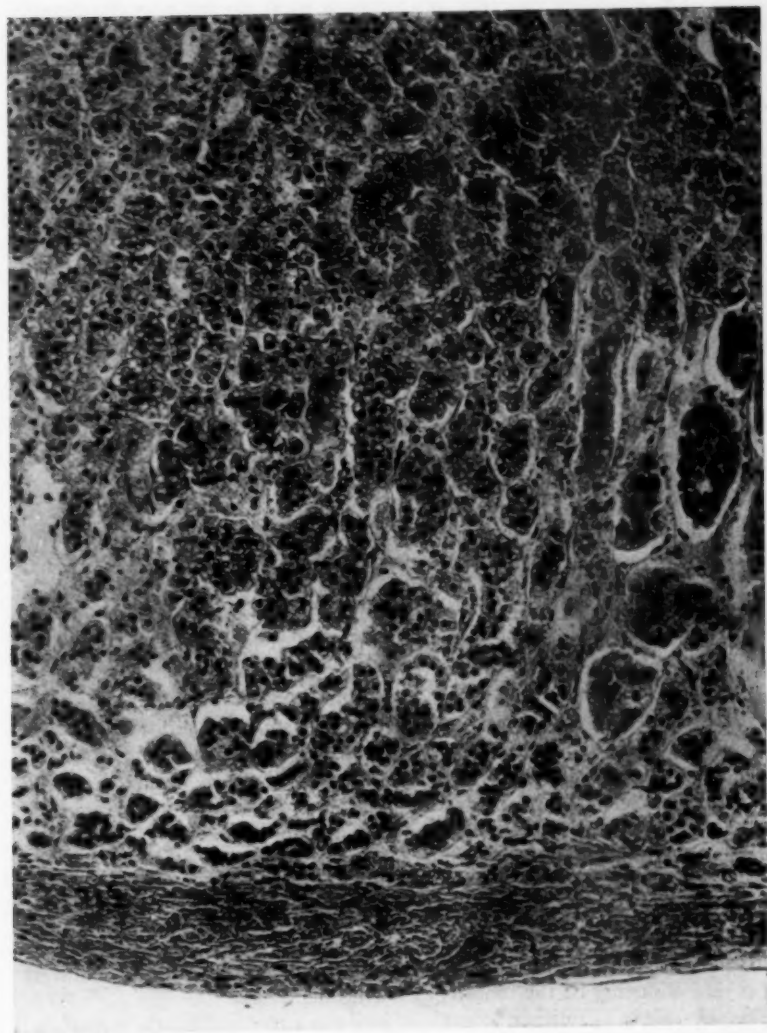


FIG. 4C. Adrenal cortex $\times 200$. (Phloxine methylene blue.) Case 1, table 1. Few focal areas of depletion of lipid but zona fasciculata is generally well-filled with lipid.

examined in seven cases; two showed a definite increase in the eosinophilic myeloid series (out of proportion to the other myeloid elements). Other findings of postmortem examinations of these cases do not appear relevant.

DISCUSSION OF GROUP I

Death during an attack of bronchial asthma is comparatively rare. Unger⁴ recently estimated that approximately 200 autopsy reports of deaths during an acute attack had been published up to that time and he discussed the reasons for the paucity of such reports. The present series adds 13 cases. One patient was a six year old male with multiple extrinsic allergies. There have been only scattered reports of death from extrinsic bronchial asthma in the first decade of life.^{10, 11} Five patients, 49 years of age or more, died in status asthmaticus less than one year after the onset of asthmatic symptoms. The rapid and fatal course of asthma in some patients, when its onset occurs in later decades, has been noted.³ One patient in this series had a pneumothorax and subcutaneous and mediastinal emphysema. This complication has been previously described in death resulting from asthma.^{12, 13} Two patients developed peripheral vascular collapse on the day of death; in these cases, asphyxia may have produced the state of shock.

Morphine was administered to three of five patients who were considered to have heart failure. None of these patients had the anatomical changes of cardiac failure. Death following morphine therapy to patients in status asthmaticus has been frequently reported.^{14, 15, 16, 17, 18} Such therapy has been decried for many reasons. On the whole, morphine tends to depress the respiratory rate, diminish the tidal volume, and decrease the minute volume of respiration, thus increasing the degree of hypoxia, decreasing the cough reflex and preventing effective expectoration. The latter may lead to segmental atelectasis. At times, morphine appears to increase the degree of nausea and vomiting and of bronchospasm. In addition, there is always the possibility of hypersensitivity and addiction to the drug itself.

The pathological findings of these cases where death occurred during an attack of bronchial asthma were essentially similar to those previously reported. Thieme and Sheldon⁸ stated that the pathologic diagnosis of bronchial asthma can be made only when the majority of the following criteria are present: (1) hyaline thickening of the basement membrane of medium-sized bronchi, (2) hypertrophy of the muscles of medium-sized bronchi, (3) mucous plugs in large and small bronchi, (4) eosinophilic infiltration, (5) sacculation of the bronchi, and (6) excessive production of mucus and widening of the mouths of the bronchial glands.

Emphysema was uniformly present in these cases and in the great majority of reported cases. In discussion of a Cabot case, Mallory¹⁹ stated that a significant grade of emphysema was rarely found in cases of known asthma at autopsy unless other pulmonary complications were present. Atelectasis has been uncommonly reported and occurred in only one case of

this group. Mucous plugs were present in each case. The frequent occurrence of focal groups of neutrophils in both the lumen and wall indicates the presence of focal acute bronchitis superimposed on bronchial asthma. The additional exudate increases bronchial obstruction and may initiate the development of bronchopneumonia in atelectatic areas of the lungs.²⁰ Desquamation of epithelial cells appears related to three factors: (1) the expulsion of mucus, (2) the presence of infection of the bronchial tree, and (3) postmortem autolysis. Since mucus in the lumen is frequently seen attached to goblet cells, expulsion of the mucus is probably accompanied by desquamation of cellular elements of the epithelium. Moore²¹ and Hilding²² suggested that a metamorphosis of ciliated columnar cells to goblet cells occurred in bronchial asthma and was of basic importance because it hindered the expulsion of mucus from the bronchial tree. Their evidence favoring this concept included (1) the marked prominence of goblet cells in the bronchial epithelium of patients dying in status asthmaticus, and (2) the appearance of many distended goblet cells in the epithelium of a nostril of a rabbit subsequent to its experimental closure. In our series, goblet cells were distended and prominent, but it is not certain that there was any increase in number. Chronic inflammation of the bronchi was frequently seen. The presence of acute and chronic bronchitis appears to play an important part in the eventual course of some patients with bronchial asthma (Group II). Hypertrophy of the musculature of middle-sized bronchi has been frequently described in the past.^{23, 26} However, Cooke²⁴ pointed out that such hypertrophy occurs as frequently in chronic bronchitis as in bronchial asthma and may even be greater in the former. Mallory²⁵ has questioned the presence of true hypertrophy in bronchial asthma and feels that the apparent thickening of the bronchial musculature may be the result of severe rigor mortis simulating hypertrophy. Without measurements of bronchi, it does not seem possible to state accurately that the musculature of a given bronchus is hypertrophied. There is marked variation in muscle thickness of bronchi of similar outside diameters in the same cases. The number of middle-sized bronchi available for micrometric examination in these cases was insufficient for statistical analysis.

The status of the heart in bronchial asthma has been the subject of many previous studies.^{4, 9, 26, 27, 28, 29} Disagreement has been expressed as to the presence and importance of right ventricular strain and hypertrophy in uncomplicated bronchial asthma. There has been recognition of the fact that people with asthma may have clinical signs and symptoms usually referable to cardiac failure but due to extracardiac factors.⁹ Chronic bronchitis and emphysema may produce cough, basal râles, cyanosis, dyspnea and orthopnea. The calibre of the pulmonary capillaries is decreased in the presence of emphysema and signs of increased venous pressure may result. However, in this group of uncomplicated bronchial asthma there were four patients with definite hypertrophy of the right ventricle in the absence of hyperten-

sive or valvular disease. One patient had signs, symptoms and anatomical evidence of right-sided cardiac failure. In the other three, cor pulmonale was an incidental finding so far as the clinical course was concerned. In other studies, the finding of cor pulmonale in uncomplicated bronchial asthma has been variable.

Thieme and Sheldon⁸ reported seven cases of status asthmaticus, each with central congestion of the liver. Rich and coworkers²⁰ have demonstrated that central congestion, atrophy and even central hemorrhagic necrosis of the liver may result from anoxemia or anemia. In this study, four cases had central congestion and atrophy of liver cells, one had central hemorrhagic necrosis. Blood counts were not available in two cases. There was no significant anemia in the other cases. Anatomically there was evidence of cardiac failure in only one case. It is possible that the asphyxia of attacks of bronchial asthma may be related to the development of these hepatic changes.

Particular attention was paid to lymphoid tissue and adrenal morphology in this group. In the fatal cases of bronchial asthma studied by MacDonald⁷ and Thieme and Sheldon,⁸ a persistent thymus, as a rule, was found; the lymphoid tissues were hyperplastic and the adrenal glands and the aorta were hypoplastic. These patients were considered to be of the "thymicolymphatic constitution." There has been general lack of confirmation of the presence of status thymicolymphaticus in bronchial asthma. Such changes were not found in the present group of cases.

A possible relationship between bronchial asthma and the "general adaptation syndrome" was suggested in these cases by the observation of lymphoid changes resembling those described in the "alarm reaction."²¹ Selye²² has reported the results of various workers who have been able to produce the alarm reaction in animals by different stimuli, such agents as epinephrine, histamine, decreased oxygen tension and emotional stress. Most, if not all, of these stimuli are present during attacks of bronchial asthma. The morphologic changes observed in animals during the alarm reaction are best noted in lymphoid tissue and the adrenal glands. The lymphoid changes, which consist of pyknosis and karyorrhexis of lymphocytes and phagocytosis of nuclear debris by macrophages, are marked in the thymus gland, less marked in the lymph nodes, and only slight in the spleen. These changes usually begin to appear several hours after an alarming stimulus is administered; they reach their height in approximately 24 hours. A species difference has been noted. The cortex of the adrenal gland rapidly loses its lipid after an alarming stimulus has been introduced, but regains the lipid in approximately 24 hours. In Group I, the thymus of only one case was available. It showed marked changes, similar to those to which Selye has applied the term "accidental involution." These changes consisted of marked pyknosis and karyorrhexis of thymocytes and cytophagocytosis of nuclear debris by macrophages. A mediastinal lymph node of the same case

showed moderate anthracosis and large cellular germinal centers composed of many lymphocytes, lymphoblasts and macrophages. There were moderate pyknosis and karyorrhexis of lymphocytes, and phagocytosis of nuclear debris. Some germinal centers in the spleen appeared hyalinized; others showed slight pyknosis and karyorrhexis. The adrenal glands contained a large amount of lipoid, with no evidence of depletion at the time of death. This patient, an 18 year old girl, had continuous asthma during the terminal 24 days. Sinusitis was present. Epinephrine was administered repeatedly. There was a marked blood and tissue eosinophilia; eosinophiles were found even in the interstitial tissue of the myocardium. Mucous plugs and emphysema were present. Hence, many of the so-called alarming stimuli (histamine, epinephrine, hypoxia, and emotional stress) appear to have been present over at least a period of days.

In the other cases there were variable degrees of lymphoid changes of the type described, and the amount of lipoid in the adrenal cortices was also variable. It is obvious that the controlled conditions obtainable in the experimental laboratory were not present. Rather than one "alarming stimulus" shortly before death, there were many alarming stimuli active over days and even weeks preceding death. Lymphoid and adrenal changes might be expected, therefore, to be variable. The lymphoid changes which were seen in these cases have, in the past, been considered either "toxic" or inflammatory in origin. It is possible that these changes may represent those of the "alarm reaction."

Group II (table 2): This group is composed of patients who died with diseases which frequently accompany and are possibly related to chronic bronchial asthma. Sixteen patients, 15 males and one female, have been placed in this group. All patients were in the fourth to seventh decades with the exception of one, who was 16 years of age. A history of bronchial asthma for 10 or more years was present in 13 patients, while only one patient had asthma for less than five years.

The clinical findings were generally those of emphysema, acute and chronic bronchitis, bronchiectasis, bronchopneumonia and cor pulmonale. Clinically, emphysema was diagnosed in three patients, bronchitis in four, bronchiectasis in three, and bronchopneumonia in eight. Three patients were treated as decompensated cor pulmonale; in two of these cases, diagnoses of emphysema and "compensatory polycythemia" were also made. Cor pulmonale was questioned in a fourth patient. The diagnosis of arteriosclerotic heart disease with cardiac decompensation was frequently made.

The major anatomic causes of death were: bronchopneumonia in nine patients, decompensated cor pulmonale in five patients, acute bronchitis in one patient, and secondary amyloidosis associated with chronic bronchitis and bronchiectasis in one patient. The anatomic findings were as follows: There was moderate to marked emphysema in each case. Neutrophils were present in the lumen and walls of bronchi in all cases of broncho-

TABLE II

Case No.	Sex	Age at Death	Duration of B.A.	Present Illness	Clinical Diagnosis	Anatomical Diagnosis
1	M	52	15 yrs.	Intermittent bronchial asthma 15 yrs. Increasing dyspnea and orthopnea for 2 weeks. Marked cyanosis, emphysema and distended neck veins. Improved after digitalis, morphine and oxygen. Died suddenly following morning.	Bronchial asthma. Emphysema. Cardiac failure, left and right. ? Hypertensive heart disease. ? Cor pulmonale.	Emphysema. Chronic bronchitis. Bronchopneumonia. Cor pulmonale.
2	M	63	8 yrs.	Chronic severe asthma. Exhaustion in last 2 weeks. Morphine 8 hrs. and 24 hrs. before death.	Arteriosclerotic heart disease. Coronary thrombosis. Chronic bronchitis. Bronchial asthma.	Emphysema. Bronchiectasis. Chronic bronchitis. Bronchopneumonia. Amyloidosis.
3	M	44	33 yrs.	Severe attack of "asthma" day before death. Treated with morphine. Entered in peripheral vascular collapse. Marked cyanosis. Diffuse rales in chest.	Chronic bronchitis. Bronchial asthma. Acute cardiac failure. ? Acute adrenal insufficiency.	Emphysema. Chronic bronchitis. Squamous metaplasia of bronchi. Bronchopneumonia, organizing. Cor pulmonale. Amyloidosis.
4	M	65	5 yrs.	Intermittent bronchial asthma 5 yrs. Cough, fever 3 days. Pneumococcus, type III, in sputum. Dyspnea, cyanosis, coma.	Bronchial asthma. Bronchopneumonia.	Emphysema. Bronchopneumonia. Pulmonary fibrosis.
5	M	57	30 yrs.	Hospitalized twice in last month because of bronchopneumonia. Died after second admission.	Bronchial asthma. Bronchitis. Bronchopneumonia, recurrent. Pulmonary fibrosis. Cor pulmonale.	Emphysema. Bronchiectasis. Chronic bronchitis. Bronchopneumonia. Pulmonary fibrosis. Cor pulmonale.
6	F	66	40 yrs.	Intermittent bronchial asthma 40 years. More severe in last 6 years. Exertional dyspnea, ankle edema, for last 6 months. Developed bronchopneumonia.	Bronchopneumonia. Arteriosclerotic heart disease, with cardiac failure. Bronchial asthma.	Emphysema. Chronic bronchitis. Bronchopneumonia. Arteriosclerotic heart disease. Cardiac failure, moderate.
7	M	64	10 yrs.	Intermittent bronchial asthma 10 years. Exertional dyspnea 1 year. Upper respiratory infection and cough 3 days. Slight ankle edema. Sudden dyspnea and death.	Arteriosclerotic heart disease, with cardiac failure, slight. Bronchial asthma.	Emphysema. Bronchiectasis. Chronic bronchitis. Cor pulmonale. Cardiac failure, right, moderate. Bleeding gastric ulcer.
8	M	58	44 yrs.	Productive cough 1 week. Occasional hemoptysis. Died soon after admission.	Bronchial asthma. Pulmonary fibrosis. Bronchiectasis. Arteriosclerotic heart disease.	Emphysema. Chronic bronchitis. Bronchopneumonia. Arteriosclerotic heart disease. Cardiac failure.

TABLE II—Continued

Case No.	Sex	Age at Death	Duration of B.A.	Present Illness	Clinical Diagnosis	Anatomical Diagnosis
9	M	16	14 yrs.	Medicolegal case. Bronchial asthma, severe in last 2 months. Continuous dyspnea one month. Died in bed at home.	Bronchial asthma.	Emphysema slight. Chronic bronchitis. Cor pulmonale. Cardiac failure, right.
10	M	62	10 yrs.	Bronchial asthma for 10 yrs. Narcolepsy for 10 yrs. Entered in coma and died 6 hours after admission.	? Post-encephalitic narcolepsy. ? Brain tumor. ? Cerebral accident. Bronchial asthma.	Emphysema, slight. Chronic bronchitis. Cor pulmonale. Cardiac failure, right, marked. Bronchopneumonia.
11	M	53	52 yrs.	Right-sided cardiac failure for 6 years. Terminally, not responsive to therapy.	Bronchial asthma. Emphysema. Bronchiectasis. Cor pulmonale. Polycythemic heart disease.	Emphysema. Cor pulmonale. Calcific aortic stenosis. Cardiac failure, right, marked.
12	M	69	"many years"	Cough and dyspnea in last week with evidence of bronchopneumonia.	Bronchial asthma. Bronchopneumonia.	Emphysema. Chronic bronchitis. Bronchopneumonia. Cor pulmonale
13	M	68	60 yrs.	Shaking chill and left chest pain 1 week before admission. Signs of consolidation of left lower lobe. Bronchoscopy was followed by increasing dyspnea and cough.	Bronchial asthma. Emphysema. Bronchiectasis. Bronchogenic carcinoma. ? Unresolved pneumonia. Arteriosclerotic heart disease. Cardiac failure, minimal.	Emphysema. Bronchopneumonia, organizing. Cor pulmonale.
14	M	70	"many years"	Productive cough and dyspnea for 4 days. Rales at both bases. No response to therapy.	Bronchopneumonia. Bronchial asthma.	Emphysema. Acute bronchitis. Chronic bronchitis.
15	M	45	35 yrs.	Constant asthma last 10 yrs. Signs of cardiac failure in last 4 months.	Arteriosclerotic heart disease. Cardiac failure, left and right. Chronic bronchial asthma. Cor pulmonale. Polycythemia. Bronchiolitis. Bronchopneumonia.	Emphysema. Chronic bronchitis. Cor pulmonale. Arteriosclerotic heart disease. Cardiac failure, right, marked. Bronchopneumonia.
16	M	66	25 yrs.	Asthma from 8 months of age to 25 yrs. Died with bronchopneumonia, clinically.	Bronchial asthma. Bronchopneumonia.	Emphysema. Chronic bronchitis. Bronchopneumonia, organizing. Cor pulmonale.

pneumonia and were present in large numbers in one case without pneumonia. Many lymphocytes and plasma cells were present in bronchial walls in 13 cases. In these cases, peribronchial fibrosis was observed. Bronchiectasis was found in two patients, one of whom also had large deposits of amyloid in the kidneys, spleen, liver and adrenals. Small amounts of mucus were found in the bronchi in the case of acute bronchitis without bronchopneumonia and in one other patient. In the acute bronchitis, the mucus took the form of Curschmann's spirals. In this case and in a case of bronchopneumonia, there was marked folding of the epithelium. The basement membrane was thickened and hyalinized in 13 patients; in three, it was thin and wavy. A few eosinophiles were seen in the walls of three cases. The muscle layer appeared prominent. In association with the widespread bronchopneumonia noted in nine cases, marked organization and pulmonary fibrosis were also frequently observed. Pulmonary atherosclerosis was seen in two cases, in only one of which was there hypertrophy of the right ventricle.

The heart showed anatomical changes in 13 of the 16 patients of this group. In 11 cases, the right ventricle measured 5 mm. or more in thickness in the absence of known hypertension. The heart weight of these cases varied from 240 to 660 gm., and averaged 445 gm. In two of these cases there was additional cardiac pathology; one had calcific aortic stenosis and the other had moderate focal interstitial fibrosis in the myocardium in association with coronary atherosclerosis. In the latter two cases, decompensated cor pulmonale was diagnosed clinically. There was anatomic evidence of right-sided cardiac failure in five patients. The 16 year old patient is of particular interest in that he succumbed to cardiac failure associated with cor pulmonale after an 18-month history of bronchial asthma. The lungs of this patient showed only bronchial and emphysematous changes. Two patients had arteriosclerotic heart disease; death was due to widespread bronchopneumonia and terminal cardiac failure.

DISCUSSION OF GROUP II

These patients were grouped together because of the frequency with which they followed a similar pattern of clinical and pathologic findings. The pattern consisted of emphysema, chronic bronchitis with superimposed bronchopneumonia, pulmonary fibrosis and cor pulmonale. The combination of emphysema, bronchopneumonia and pulmonary fibrosis was often accompanied by hypertrophy of the right ventricle. Valvular or coronary artery disease superimposed on hypertrophy of the right ventricle appeared to be two important factors in the production of cardiac decompensation. In two cases, the clinical diagnosis of decompensated cor pulmonale was made and each had additional cardiac pathology. Two patients had bronchiectasis. Amyloidosis, a rare complication of chronic bronchitis or bronchiectasis, was found in two patients.

Description of microscopic changes in this group is limited to the bronchi. Evidence of chronic inflammation was found in the majority of cases. Thickening and hyalinization of the basement membrane were seen more frequently in this group than in Group III, where death occurred from intercurrent disease. This suggested that such changes may be related to chronic inflammation of the bronchial tree rather than to asthma *per se*. In the patient with acute bronchitis, Curschmann's spirals and marked folding of the epithelium were present. Others have pointed out that neither finding is specific for asthma and that either may be seen in other diseases.^{2, 8} Eosinophiles were infrequently seen in these cases.

Group III (table 3): Of the 46 patients, 17 died because of intercurrent disease. This group was studied separately to note whether any frequent, persistent or pathognomonic anatomic changes occurred in patients who had a long history of bronchial asthma but died of unrelated diseases.

In this group there were 12 males and five females ranging from 13 to 87 years of age. This history of asthma varied from two to 81 years. A clinical diagnosis of an active attack of bronchial asthma was made in four patients. In other respects, the clinical diagnoses and findings were related to a history of bronchial asthma and to the intercurrent diseases.

The major anatomic causes of death included lobar pneumonia in four patients; hypertensive arteriosclerotic heart disease with cardiac failure in three; and, in one each, rheumatic heart disease with cardiac failure, acute glomerulonephritis, periarteritis nodosa, arteriosclerotic heart disease with cardiac failure, pulmonary infarct, hemorrhagic encephalopathy, chronic recurrent acute cholecystitis, malignant nephrosclerosis associated with intercapillary glomerulosclerosis, and a fracture complicated by bronchopneumonia.

The relevant anatomic findings in this group are presented at this time. Pulmonary emphysema was marked in five cases, moderate in nine, and absent in three. In three patients, the number of middle-sized bronchi available for examination was insufficient. The bronchi did not contain mucous plugs. The epithelium was not remarkable except for squamous metaplasia and marked desquamation in one case. Goblet cells and mucous glands were not active. The basement membrane was thickened and hyalinized in five patients. A variable number of plasma cells and lymphocytes was seen in the walls of the bronchi; these cells were numerous in seven cases. In one many eosinophiles were present; scattered eosinophiles were seen in only three other cases of this group. Bronchial musculature was questionably thickened and the cartilage did not appear remarkable. There was no demonstrable change in pulmonary arterioles. Four patients had a right ventricle with a thickness of 5 mm. or more in the absence of valvular disease or hypertrophy of the left ventricle. In none was there evidence of right-sided cardiac failure, clinically or anatomically. Mitral stenosis was present in one patient; hypertensive arteriosclerotic heart disease in six

TABLE III

Case No.	Sex	Age at Death	Duration of B.A.	Present Illness	Clinical Diagnosis	Anatomical Diagnosis
1	F	40	6 yrs.	Erythema nodosum and rheumatic fever 6 years ago. Bronchial asthma 6 years. Asthma worse in last 6 months. Transient ankle edema. Hypertension, dyspnea and cyanosis last few weeks.	Bronchial asthma. Bronchopneumonia. Hypertensive heart disease. ? Pericarditis nodosa.	Acute glomerulonephritis. Emphysema. Chronic bronchitis. Organizing bronchopneumonia. Cor pulmonale. Cardiac failure.
2	M	32	4 yrs.	Was hospitalized 1 month before death for bronchial asthma. Was discharged. Three hours before readmission, had sudden dyspnea and cyanosis. Entered in extremis and died in few hours.	Bronchial asthma. Chronic bronchitis. Emphysema. Status asthmaticus. ? Acute cardiac failure. ? Massive collapse.	Pulmonary infarct. Emphysema. Cor pulmonale. Squamous metaplasia of bronchi.
3	F	45	8 yrs.	Asthmatic breathing the day before delivery. Dyspnea and cyanosis increased for 2 days after delivery. Patient went into peripheral vascular collapse terminally.	Post-partum. Bronchitis. Bronchial asthma. Emphysema.	Lobar pneumonia, post-partum. Emphysema.
4	F	67	"yrs."	Many hospital admissions for asthma. Cough, dyspnea, orthopnea in last month. B.P. 190/80. Died in marked cardiac failure.	Bronchial asthma. Hypertensive arteriosclerotic heart disease.	Hypertensive arteriosclerotic heart disease. Cardiac failure. Bronchopneumonia.
5	M	56	10 yrs.	Weakness for 2 years. Cerebral accident, terminally.	Coronary occlusion. Cardiac failure. ? Cerebral thrombosis.	Hemorrhagic encephalopathy. Emphysema. Cor pulmonale. Arteriosclerotic heart disease. Cardiac failure.
6	M	82	34 yrs.	Died in peripheral vascular collapse 5 days after cholecystectomy.	Cholecystitis with cholelithiasis. Bronchial asthma.	Chronic recurrent acute cholecystitis. Emphysema.
7	M	58	30 yrs.	Mild diabetes mellitus. Azotemia in last year of life. Terminally developed cardiac failure, hypertension and "asthma" not responsive to therapy.	Diabetes mellitus. Benign nephrosclerosis. Azotemia. Arteriosclerotic heart disease. Cardiac failure. Bronchial asthma.	Inter-capillary glomerulosclerosis. Benign nephrosclerosis. Malignant hypertension. Hypertensive arteriosclerotic heart disease. Cardiac failure. Emphysema.
8	M	60	50 yrs.	Died after 1 week of lobar pneumonia.	Lobar pneumonia. Bronchial asthma.	Lobar pneumonia. Cor pulmonale.
9	M	72	23 yrs.	Marked cardiac failure in last month.	Generalized arteriosclerosis. Arteriosclerotic heart disease. Emphysema. Chronic bronchitis. Bronchial asthma.	Hypertensive arteriosclerotic heart disease. Cardiac failure. Chronic bronchitis. Bronchopneumonia. Emphysema.

TABLE III—Continued

Case No.	Sex	Age at Death	Duration of B.A.	Present Illness	Clinical Diagnosis	Anatomical Diagnosis
10	F	44	41 yrs.	"Pleurisy" 1 month before admission. Cough and fever 9 days, severe recurrent "asthma" 3 days before admission. Found in severe cardiac failure; did not respond to therapy.	Rheumatic heart disease, probably with mitral stenosis. Bronchial asthma. Cor pulmonale.	Rheumatic heart disease with mitral stenosis. Cor pulmonale. Cardiac failure. Chronic bronchitis. Bronchopneumonia, organizing.
11	M	52	15 yrs.	Died 10 days after onset of lobar pneumonia.	Lobar pneumonia. Bronchial asthma. ? Bronchiectasis.	Lobar pneumonia. Cor pulmonale.
12	M	13	11 yrs.	Signs and symptoms of space-occupying lesion in brain. No recent asthmatic attacks.	Brain tumor.	Glioma of pons.
13	M	59	2 yrs.	Chronic cough 15 yrs. Severe paroxysms of asthma for 2 yrs. 8 hospital admissions in last year. Developed bilateral foot drop and hematuria. Eosinophiles varied from 1 to 62%, W.B.C. 20,000-25,000. Muscle biopsy negative for periarthritis nodosa. Found dead in bed.	Bronchial asthma. Bronchitis. Bronchiectasis. Emphysema.	Periarthritis nodosa—vessels of peroneal nerve. Arteriosclerotic heart disease. Acute and chronic bronchitis. Pulmonary fibrosis. Emphysema. Cor pulmonale.
14	F	70	20 yrs.	Died several weeks after a fracture of the pelvis.	Bronchial asthma. Decubiti. Pulmonary infarction. Multiple fractures of pelvis. Emphysema.	Fracture of left pubic ramus. Bronchopneumonia. Acute focal colitis. Decubiti. Emphysema.
15	M	71	14 yrs.	Cardiac failure in last 6 months.	Bronchopneumonia. Arteriosclerotic heart disease with congestive failure.	Hypertensive arteriosclerotic heart disease. Cardiac failure. Chronic bronchitis. Bronchopneumonia. Emphysema.
16	M	62	35 yrs.	Upper respiratory infection 2 weeks before admission with increase in asthma following it. Died in shock soon after admission.	? Acute myocardial infarction. ? Bronchopneumonia. Acute bronchial asthma.	Lobar pneumonia. Hypertensive arteriosclerotic heart disease. Emphysema.
17	M	87	81 yrs.	Increasing cardiac failure in last 10 months.	Hypertensive arteriosclerotic heart disease. Bronchopneumonia. Hypochromic microcytic anemia. Punch cytostomy.	Hypertensive arteriosclerotic heart disease. Cardiac failure. Cystostomy.

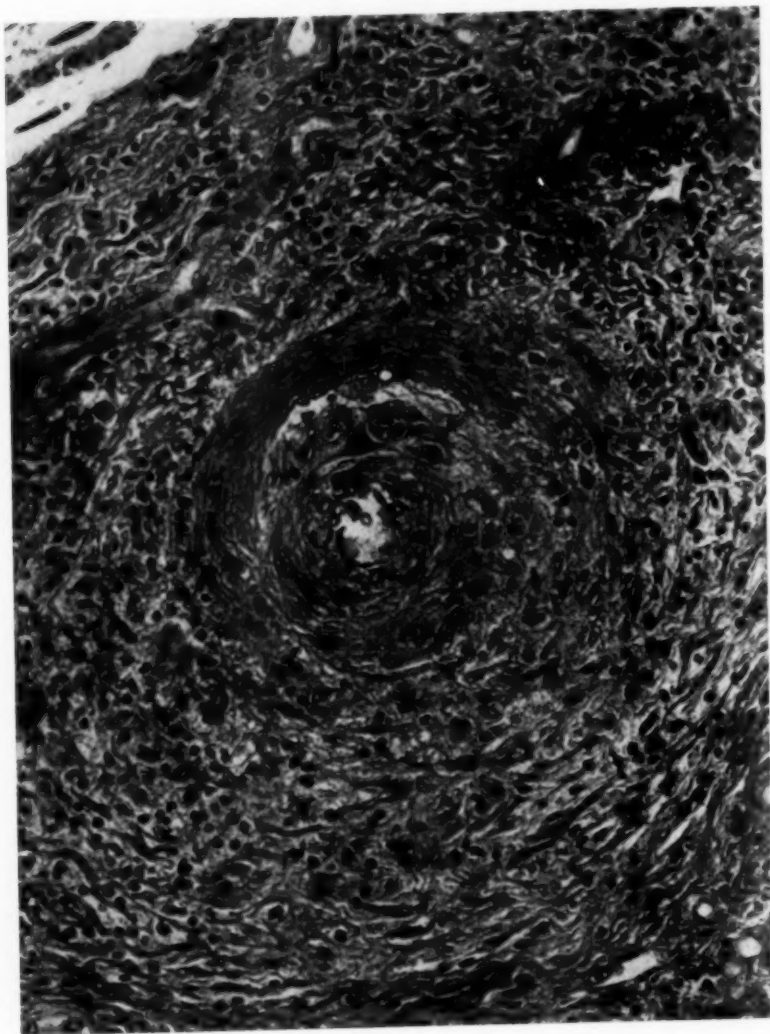


FIG. 5. Artery accompanying peroneal nerve $\times 400$. (Phloxine methylene blue.) Case 13, table 3. The wall is thickened markedly. Fibrosis is present and there is infiltration by many eosinophiles.

patients. The average heart weight, excluding that of the 13 year old patient and those with hypertension or valvular changes, was 355 gm., with variation from 240 to 480 gm. Lymphoid tissue was not prominent in the lungs. In one patient, a "sarcoid" reaction was found in a mediastinal lymph node. The kidneys of one patient revealed acute glomerulonephritis. One patient (Case 13, Group III) had lesions of periarteritis nodosa in the vessels accompanying a peroneal nerve. Figure 5 illustrates this lesion.

DISCUSSION OF GROUP III

Study of these patients who died of intercurrent disease revealed no pathognomonic findings identifiable with bronchial asthma. Most patients had pulmonary emphysema. In at least one-half of the cases, the basement membrane was not thickened or hyalinized to an appreciable degree. Chronic inflammatory cells, lymphocytes and plasma cells were seen in the walls of the bronchi in approximately 50 per cent of the cases; eosinophiles were found in bronchial walls in 25 per cent of the cases. The right ventricle was hypertrophied, in the absence of other cardiac pathology, in a similar proportion of cases.

Of four patients clinically considered to have terminal attacks of bronchial asthma, three were found to have lobar pneumonia. The fourth had a small pulmonary infarct.

Hypersensitivity has been a suggested pathogenesis for a number of the diseases which occurred in this group. Rich^{33, 34} presented evidence that periarteritis nodosa is a manifestation of hypersensitivity. Glomerulonephritis and rheumatic fever have long been considered as possibly due to a hypersensitivity. Such a pathogenesis has also been suggested for amyloidosis³⁵ and sarcoidosis.³⁶

According to the theories of the "general adaptation syndrome," the so-called diseases of adaptation occur as a result of a series of alarm reactions over an extended period of time.^{31, 32} Among these "diseases of adaptation" are hypertension, periarteritis nodosa, rheumatic fever and glomerulonephritis. Bronchial asthma appears to be a disease in which there are a number of possible alarming stimuli during an attack. From the nature of the disease, many attacks occur over a long period of time. Possible morphologic evidence of the alarm reaction during status asthmaticus was presented in the first group. If the theory of the diseases of adaptation can be applied to man, one might expect to find in bronchial asthma an increased incidence of these diseases. Wilson and Alexander,³⁷ in 1945, analyzed all reported cases of periarteritis nodosa and stated that bronchial asthma had been present in 18 per cent of the cases. In this group (III) of patients with bronchial asthma, one had periarteritis nodosa, two had evidence of rheumatic heart disease, five had essential hypertension, and one had acute glomerulonephritis as well as a history of rheumatic fever. Further studies

of status asthmaticus for evidence of the alarm reaction and studies of the frequency of occurrence in bronchial asthma of the so-called diseases of adaptation may prove to be valuable.

SUMMARY AND CONCLUSIONS

A clinicopathologic study of 46 patients with bronchial asthma is presented. These patients were divided into three groups on the basis of anatomical findings. The groups are: (I) those patients whose death occurred during an attack of bronchial asthma; (II) those patients who died because of diseases which frequently accompany and may be related to bronchial asthma; and (III) those patients who died because of intercurrent diseases.

Group I: Clinical and pathologic findings on 13 patients showed that death was due to an attack of bronchial asthma. The pathologic changes resulting from an attack of this disease are analyzed. The bronchial, pulmonary, cardiac, hepatic, lymphoid and adrenal changes are described. The lymphoid and adrenal changes seen in status asthmaticus are suggestive of the "alarm reaction."

Group II: Findings on 16 patients showed that death was due to a pattern of diseases related to bronchial asthma, the fundamental elements of which were chronic bronchitis and emphysema, often associated with bronchopneumonia, pulmonary fibrosis and cor pulmonale. It is noted that cor pulmonale was more frequent in this group than in uncomplicated bronchial asthma. Cardiac decompensation appears especially likely to develop in the presence of coronary artery disease or valvular disease superimposed on hypertrophy of the right ventricle.

Group III: Death due to intercurrent disease was manifested in 17 patients. No pathognomonic anatomic findings relatable to bronchial asthma were found. Emphysema was present in the majority of cases. There was evidence of chronic bronchitis in approximately 50 per cent of the cases. Eosinophiles were found in bronchial walls in one out of every four cases.

In this group, there were anatomic findings of periarteritis nodosa, rheumatic heart disease, glomerulonephritis, amyloidosis and sarcoid. Hypersensitivity has been suggested in the past as the pathogenesis for each of these diseases. With the exception of the latter two diseases, these diseases have been included in the theories of the general adaptation syndrome.

It is noted that "alarming stimuli" (histamine, epinephrine, hypoxia and emotional stress) appear to be present during attacks of bronchial asthma. In animals, such recurrent stimuli have produced diseases considered by some to be "diseases of adaptation." The coexistence of these diseases with bronchial asthma, in the light of the morphologic evidence of the "alarm reaction," is of considerable interest. Further studies on the frequency of occurrence of these diseases in people with asthma are in progress.

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GOLD THERAPY IN EARLY RHEUMATOID ARTHRITIS *

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IF rheumatoid arthritis is ever to be controlled completely and permanently, it would seem reasonable to suppose that such a result would have to be achieved during the comparatively early stages of the disease; that is, before marked crippling caused by joint destruction, ankylosis and deformity has taken place. In the early months of rheumatoid arthritis, apparently up to one year, the disease is nearly always completely reversible. It may be completely reversible even later if joint destruction has not occurred. This characteristic of rheumatoid arthritis has been stressed recently by Hench in his Heberden Oration.¹

Much has been written in medical literature concerning the treatment of rheumatoid arthritis with this or that remedy, but not nearly enough emphasis has been placed on the *time factor* in relation to prognosis and the effectiveness of any form of therapy. To be sure, Forestier and Certoncin² pointed out the superior results achieved with gold therapy when treatment was started early in the disease, and a few others^{3,4} have made reference to the importance of early treatment. However, the majority of investigators have been satisfied to publish a large unclassified group of cases of variable duration in which gold salts or some other agent has been used with apparently beneficial results.

The announcement of Hench, Kendall, et al.⁵ on the remarkable effect of Cortisone and ACTH on the reversibility of rheumatoid arthritis has led many practitioners to believe that gold salts and other therapeutic agents for this disease are about to be replaced by these newer agents. However, because of certain delays which are being encountered in the distribution of both Cortisone and ACTH, it seems reasonable to suppose that the present methods of therapy, including gold salts, will remain in use for some time to come.

Few studies on chrysotherapy have been adequately controlled. This is understandable, for it is difficult to carry out a perfectly controlled experiment on patients with rheumatoid arthritis inasmuch as the disease differs so widely in the severity and duration of the morbid process.

The present study was undertaken in order to compare the results obtained in early cases by conventional methods of treatment, such as rest, good hygiene, salicylates, physical therapy, and orthopedic measures, with

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those obtained by conventional measures plus chrysotherapy. This investigation has been carried out on the following plan:

(1) The only gold cases included are 106 patients who developed rheumatoid arthritis less than one year before gold therapy was instituted. With the exception of four who received a minimum of 350 mg. of gold salts, all received 500 mg. or more of gold salts. These patients comprise the "Gold Treated Group."

(2) Eighty-three patients who were treated by conventional methods but without gold salts were used as controls. These are designated the "Control Group."

(3) No cases were included in this study unless they had been under observation for more than 18 months. Many were observed for a period of five years or more.

(4) Patients whose rheumatoid symptoms and findings were associated with psoriasis, ulcerative colitis, Felty's syndrome, or Reiter's syndrome were excluded.

(5) The "Therapeutic Criteria in Rheumatoid Arthritis"^{*} was used as a guide in this study. The final evaluation of therapeutic results in both the "Gold Treated Group" and in the "Control Group" was made in accordance with its standards. The term "complete remission," as used in this investigation, covers only those cases which meet the definition set up by the "Therapeutic Criteria." These criteria are summarized in chart 1.[†]

Since the introduction of chrysotherapy into this country, its value has been the subject of some controversy. While a great majority of writers have been convinced that gold salts influence favorably the course of rheuma-

CHART I
Response of Rheumatoid Activity to Therapy[†]

Grade	Systemic Signs	Signs of Joint Inflammation	Signs of Extra* Articular Activity	Remaining Impairment of Joint Mobility	E.S.R.	Articular Enlargement or Deformity	Roentgenologic Signs
I Complete remission	0*	0*	0*	Only due to irreversible changes	0*	Only due to irreversible changes	No progression
II Major improvement	Only* moderate E.S.R. and/or vasomotor imbalance	Only* minimum residual joint swelling (no new sites)	Minimum (no new sites)	Only consistent with minimum residual activity	Moderate elevation	Same as above	No progression
III Minor improvement	Decreased*	Only* partially resolved (no new sites)	Decreased* (no new sites)	In relation to residual inflammation	May be elevated	May be present	No progression
IV Unimprovement	Undiminished*	Same* or worse	*Same* or new sites or exacerbation	Same, better or worse	Any rate	Present or not	Changes indicative of progression

* Indicates criteria required to be present.

† This chart is taken from "Therapeutic Criteria in Rheumatoid Arthritis" by Steinbrocker, Traeger and Batterman.

toid arthritis, a few have maintained that the ultimate results were approximately the same when the disease was treated by traditional methods. The latter group has further claimed that any advantage that gold salts may have in inducing favorable results is offset by the potential toxic effects attending its use. A recent statement by the American Rheumatism Association summarizes the present status of chrysotherapy:

"There is a fairly uniform agreement—but with some very competent dissenters—that gold is the one agent which has been shown to change the course of rheumatoid arthritis in a significant number of patients."* * *

METHODS OF MANAGEMENT

In this study every patient with an established diagnosis of rheumatoid arthritis received a preliminary blood count and urinalysis. These tests were repeated every two to four weeks while gold salts were being administered. Platelet counts were made frequently. The erythrocyte sedimentation rate was determined, with a few exceptions, by the Westergren method before treatment was started and was repeated every two to three months while treatment was continued. Roentgenograms were taken of the affected joints in a majority of cases.

Aurothioglucose— $C_6H_{11}O_5S\ Au$ —(Solganal) and gold sodium thiomalate— $C_4H_3SAu\ Na_2O_4$ —(Myochrysine) were the salts usually employed, although several other preparations were occasionally used.† In rare instances, the same patient received both Solganal-B Oleosum and Myochrysine. As far as could be judged, there was no significant difference between the two gold salts in respect to either therapeutic effect or toxicity.

The usual procedure has been to start the patient on 10 mg. of gold salts and to increase the dosage gradually to a maximum of 50 mg., and in some cases to 100 mg. The interval between doses has been one week. The treatment has usually been continued until a total dosage of 1,000 to 1,500 mg. has been administered. Many of the patients received several courses and, more recently, gold-treated patients in remission have been given maintenance doses of gold at intervals of two weeks to one month. If, after receiving 1,000 to 1,500 mg., the patient has not shown definite clinical improvement and a fall in sedimentation rate, we are disposed to discontinue gold therapy on the theory that in this particular case the patient will not be benefited by it.

ANALYSIS OF CASES

In the combined group of 189 cases the ratio of females to males was 2:1. The average age of the gold treated group was 40.7 years; that of the controls was 42.6 years. Slightly over 10 per cent were 60 years of age or older.

* This statement was made before the publication by Hench and his co-workers of their results with Cortisone and ACTH.

† We are greatly indebted to Merck & Company for supplying Myochrysine for this study and to the Schering Corporation for Solganal-B Oleosum.

The sedimentation rate was elevated significantly in a high percentage of cases. Ninety-nine per cent of the combined groups had disability ranging from slight impairment of function to almost complete incapacitation.

The general status of patients before treatment is shown in table 1.

TABLE I
Status of Patients before Treatment

	Gold	Controls
Average age—years.....	40.7	42.6
Sedimentation rate	%	%
Normal.....	6.7	14.5
Elevated.....	93.3	85.5
Degree of disability		
None.....	0.9	1.2
Slight to severe.....	93.6	98.8
Extreme.....	5.5	0.0

IMMEDIATE EFFECT OF GOLD THERAPY

It is recognized that rheumatoid arthritis is in many instances an incurable disease. The purpose of treatment, therefore, is to obtain a remission of symptoms even though this remission may be of uncertain duration.

It was the finding of Short and Bauer⁹ that patients whose treatment (without gold) was initiated within six months after the recognized onset of the disease showed more or less improvement in 81 per cent of the cases, while those treated during the second six months of their illness showed improvement in only 60.6 per cent. It has also been noted by one of the writers (R.L.C.)¹⁰ in a previous publication that patients who were treated

TABLE II
Immediate Response to Therapy
Gold Treated Cases Compared with Controls*

Duration of disease.....	1-6 Months		7-12 Months	
	Gold (61) %	Controls (47) %	Gold (45) %	Controls (36) %
Remission.....	78.7	29.8	48.9	16.7
Great improvement.....	11.5	27.7	37.8	38.9
Moderate improvement.....	6.5	25.7	11.1	22.2
No improvement.....	3.3	14.8	2.2	22.2

* One year has been the period arbitrarily set for the evaluation of the patient.

with gold salts early in the course of their arthritis responded much better than those who were treated later.

In the present study the immediate response of 106 patients treated early with gold salts is compared with 83 controls for a comparable period in table 2.

TABLE III
Immediate Response to Therapy
Gold Treated Cases Compared with Controls*

Duration of disease	Gold treated (106) %	Twelve months or less Controls (83) %
Remission	66.0	24.1
Great improvement	22.8	32.5
Moderate improvement	8.4	25.4
No improvement	2.8	18.0

* One year has been the period arbitrarily set for the evaluation of the patient.

Remission occurred in 78.7 per cent of the gold-treated patients when treatment was initiated within six months of the onset of their illness. When gold was started during the second six months of the disease the remission rate dropped to 48.9 per cent. The control group showed a similar change: 29.8 per cent of remissions among those treated during the first six months, versus 16.7 per cent in those treated during the second six months.

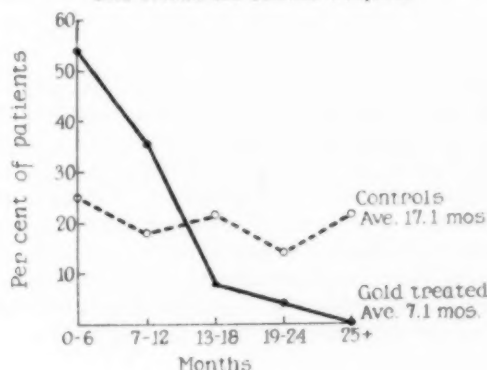
A consolidation of table 2 is seen in table 3.

The overall remission rate for the gold-treated group was 66 per cent. The figure for the controls was 24.1 per cent. Only 2.8 per cent of the gold group failed to show some improvement at the end of the first year. Eighteen per cent of the controls were unimproved. Eighty-two per cent of the controls showed some degree of improvement. This figure checks fairly closely with 74.1 per cent improvement reported by Short and Bauer⁹ for non-gold-treated early cases of rheumatoid arthritis.

EFFECT OF GOLD ON ACCELERATION OF REMISSIONS

The immediate results of gold administration in early rheumatoid arthritis indicate that this agent increases the frequency of remissions and

TABLE IV
Duration of Time (in Months) from Initiation of Treatment to Remission;
Gold Treated and Controls Compared



accelerates considerably their appearance. The evidence for this statement is found in table 4.

It is seen that in gold-treated cases 56 per cent of remissions began within six months after starting gold and that an additional 34 per cent occurred during the second six months. Altogether, 90 per cent of remissions occurred within a year after initiating chrysotherapy. All remissions which have occurred in this group have done so within two years. The control group shows a very different curve. At the end of six months only 25 per cent had remitted and at the end of a year the figure was 44 per cent. The average period from initiation of treatment to remission in the gold group was 7.1 months; in the controls, 17.1 months. Ten months is a very significant figure to a patient with arthritis!

RELAPSES

The clinical course of rheumatoid arthritis is usually marked by remissions and relapses. It is agreed generally that the longer a series of cases is followed, the higher will be the percentage of relapses. The average period of observation for the gold-treated group was 47 months; for the controls, 53 months. During the period of observation there was no significant difference in the relapse rate between the two groups. The actual figures shown in table 5 are 28.5 per cent of relapses in the gold-treated cases, 33.3 per cent in the controls.

TABLE V
Incidence of Relapse After Treatment with Gold Salts

Results of Treatment	Relapses in Gold Treated Cases %	Relapses in Control Cases %
Remission group	26.1	33.3
Great improvement group	43.8	33.3
Both groups	28.5	33.3

The average period of time from remission to relapse, when it occurred, was the same for both groups—27 months.

END RESULTS

The *immediate results* obtained from therapy as shown in tables 2 and 3 differ from the *end results* as shown in tables 6, 7 and 8. Because of the fluctuant nature of rheumatoid arthritis, many patients, especially in the control group, had not attained remissions at the end of one year's observation. On the other hand, some of the patients in the gold-treated group who had attained remissions were destined to relapse before the final evaluation was made. The end results have been evaluated (1) in table 6 by the usual criteria, (2) in table 7 with respect to the duration of the disease at the time when treatment was initiated, and (3) in table 8 in respect to the "Therapeutic Criteria" of the American Rheumatism Association.

When the end results of treatment were evaluated according to the usual criteria, the figures shown in table 6 were obtained.

Fifty-five and seven-tenths per cent of those receiving gold salts were in remission at the time of their last examination and showed no evidence of

TABLE VI
Results of Gold Treatment at End of Observation Period

Result	Gold Treated	Controls
Remission.....	55.7	36.1
Great improvement.....	15.1	14.4
Moderate improvement.....	17.0	16.9
No improvement or worse.....	12.2	32.6

active rheumatoid arthritis. The control remission rate was 36.1 per cent. Twelve and two-tenths per cent failed to respond to chrysotherapy; of those treated by conventional methods, 32.6 per cent showed no improvement or there was evidence of progression of the disease.

The observation previously noted—that the earlier definitive treatment for rheumatoid arthritis is instituted the better the immediate and ultimate prognosis is for the patient—is supported by the figures presented in table 7.

TABLE VII
Comparison of Percentage of Remissions and Great Improvement in Relation to the Duration of Rheumatoid Arthritis (Gold Treated and Control Series)

Duration	Gold Treated %	Controls %
Six month cases.....	77.0	59.5
Twelve month cases.....	62.2	39.2

Considering the end results in the cases of six months' versus 12 months' duration, it is found that the percentage of remissions and greatly improved cases in both gold-treated and control groups is significantly higher in the six-month cases than in the 12-month cases. As in other tables, the gold-treated groups show definitely better results. This again emphasizes the importance of making an early diagnosis of rheumatoid arthritis and initiating therapy, especially gold therapy, promptly.

RESULTS ACCORDING TO "THERAPEUTIC CRITERIA"*

Finally, when the patients studied in this report were classified according to the "Therapeutic Criteria," the figures shown in table 8 were obtained.

There is a sharp decline in the percentage of remissions in both series. There is a significant increase in the number of cases relegated to the "unsatisfactory results" column.

In accordance with the "Therapeutic Criteria," any evidence of rheumatoid activity occurring after the therapeutic effect has been deemed to have been obtained (even a relapse followed by a second remission), or any radiological or other evidence of progression of the disease process, demands a

TABLE VIII
Therapeutic Response

Grade	Response	Gold Treated %	Controls %
I	Complete remission	44.8	27.7
II	Marked improvement	13.2	9.6
III	Slight improvement	5.7	8.8
IV	Unsatisfactory	36.3	53.9
		58.0	37.3

classification of the case as an "unsatisfactory result." This classification must be made regardless of the functional condition or the physical findings of the patient at the end of the observation period.

Approximately 45 per cent of those receiving chrysotherapy have been in sustained remission for a period of one to five years, while 27.7 per cent of the controls have maintained remissions for a similar period.

TOXIC REACTIONS

A serious objection to the use of gold has been the fear of toxic reactions, especially those of a more serious nature. In this series there were no fatalities in the gold-treated series. One control case died of an intercurrent infection. The percentage of toxic reactions, including mild dermatitis and transient albuminuria, was 48.6. In general, the reactions were trivial and cleared up in a relatively short time. Gold therapy was withheld at the first sign of toxicity. In the mild dermatoses gold was reinstituted upon resolution of the skin rash, in a majority of cases without further untoward reactions.

In this group of toxic reactions there were two cases of temporary alopecia and one each of purpura simplex, leukopenia, exfoliative dermatitis and enterocolitis.

In the case of patients with the more severe reactions it was considered inadvisable to reinstitute gold therapy upon the subsidence of the condition.

DISCUSSION

The results of this study afford considerable evidence that gold salts have a definite value in the treatment of early rheumatoid arthritis. The ultimate difference in results, however, between the gold-treated cases and the controls is not as marked as might have been expected. The immediate effect of gold therapy in early cases is certainly excellent. The striking acceleration of remissions as compared with the controls is clearly brought out by the figures presented.

Short and Bauer⁸ obtained a remission incidence in 37 per cent of their patients with rheumatoid arthritis who were treated without gold during the first year of their illness. This figure is almost identical with that ob-

tained in the control group of the present study (36.1 per cent). (See table 6.)

Forestier¹¹ expressed the opinion that early cases of rheumatoid arthritis respond particularly well to chrysotherapy, and Freyberg³ believes that early cases show a more favorable reaction to gold. Gardner⁴ found in his series of early cases that they reacted well to chrysotherapy, with approximately 50 per cent "cured."

Cecil, Kammerer and De Prume¹⁰ state that in a series of 235 cases of rheumatoid arthritis treated with gold salts, 31 per cent had a complete remission; however, when rheumatoid patients of less than one year's duration were treated with gold, 39 per cent achieved a complete remission.

The consensus of reports indicates that about 50 per cent of *all cases* are "strikingly improved" by chrysotherapy, with a much lower percentage maintaining remission. In the present study our remission rate for cases treated *early* with gold was 78.7 per cent while the patient was undergoing therapy or shortly after the treatment had been completed. According to the standards set by the "Therapeutic Criteria," 44.8 per cent were classified as *complete* remissions.

If remissions achieved by patients with this disease could be maintained and relapses prevented, we would be well on the way to a solution of the rheumatoid problem. Ragan and Tyson,¹² in their follow-up study of cases of rheumatoid arthritis, report an over-all relapse rate of 75 per cent. They note that there is less tendency to relapse in cases that were markedly improved than in the slightly improved cases. The inference to be drawn is that any exacerbation in an active case of rheumatoid arthritis has to be classified as a relapse. As a matter of fact, the normal course in the majority of cases of rheumatoid arthritis consists of periods of inactivity or recession of symptoms alternating with episodes of exacerbation of pain and extension of the disease to new joints. It is only when there is clinical absence of rheumatoid activity and complete remission has taken place that evidence of recurring activity constitutes a real relapse. In our series relapses occurred in 26.1 per cent of the gold-treated cases and in 33.3 per cent of the controls. Short and Bauer⁹ whose cases were followed for a longer period than ours, report a relapse rate of 46.5 per cent. If relapses could be prevented by gold therapy, then gold would have a more secure place in the therapeutic armamentarium of the disease. It is quite possible that the introduction of maintainance gold therapy, that is, a small injection of gold once a month for an indefinite period of time, will prevent a considerable number of these relapses.

In the present study the incidence of complete remissions, as very strictly defined by the "Therapeutic Criteria," is 44.8 per cent for those who received gold and 27.7 per cent for the controls (table 8).

Toxic reactions have not been a serious problem in this study. Dermatitis, usually of a mild nature, occurred in quite a number of patients; this

manifestation, however, soon cleared when gold was discontinued. Our personal belief is that skin rashes would occur in almost 100 per cent of cases if gold were continued long enough.

From time to time one reads an article on gold therapy in which the physician is advised not to resort to gold salts until all other measures have been tried. This has always seemed to us to be an irrational attitude. If gold is to be of any value in the treatment of this disease, it should be used as soon as the diagnosis of rheumatoid arthritis has been confirmed.

SUMMARY

1. The results obtained in the treatment of 106 patients with rheumatoid arthritis treated during the first year of their illness by chrysotherapy are compared with those obtained in a control group of 83 patients who were treated by conventional methods without gold.

2. All patients were under observation for a minimum period of one year after the optimum therapeutic effect was deemed to have been obtained. All were under observation for a total period ranging from 18 months to 12 years.

3. Remissions were present in 66 per cent of the gold-treated patients one year after institution of chrysotherapy; in only 24.1 per cent of the control group.

4. On the average, remissions were noted 10 months sooner in the gold-treated cases than in the controls; the actual figures are 7.1 months versus 17.1 months.

5. The incidence of remissions which are classified as *complete* and are in accordance with the "Therapeutic Criteria" of the American Rheumatism Association was 44.8 per cent in the gold group, as compared with 27.7 per cent in the controls.

6. The relapse rate was 26.1 per cent for the gold treated remissions; 33.3 per cent for the control remissions.

7. There were no fatalities among the gold-treated cases and most of the toxic reactions were of a mild nature.

CONCLUSION

Gold salts, if administered during the first year of rheumatoid arthritis, increase and accelerate the appearance of remissions.

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CARDIAC ARRHYTHMIAS PRODUCED DURING RIGHT HEART CATHETERIZATION: RE- PORT OF TWO CASES OF TRANSIENT PARTIAL RIGHT BUNDLE BRANCH BLOCK *

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SINCE Forssman¹ first passed a catheter into his own heart in 1929, the procedure of right heart catheterization has proved itself of great value in the study of the normal and pathologic physiology of the cardiovascular system. Increasing numbers of investigators are doing, or are preparing to do cardiac catheterizations. The thousands of catheterizations which have been done would tend to testify to the apparent safety of the procedure. Although only three cases of death resulting from cardiac catheterization have been mentioned in the literature, many individuals who have done large numbers of catheterizations or been in contact with persons who were doing them know of isolated instances where death either resulted from or was precipitated by the procedure. Death would seem to have been the result of arrhythmias. That arrhythmias occur is known to all who have performed the procedure and their occurrence has received some mention in the literature. We do not believe, however, that the degree and character of these arrhythmias have received the attention which they deserve. It is the purpose of this paper to report the arrhythmias which were encountered in a relatively small group of adults in whom the catheterization was done under electrocardiographic control.

The occurrence of ventricular premature contractions has been noted by many workers.^{2, 3, 4, 5, 6} Dexter³ states that five of 12 patients who had electrocardiograms recorded at frequent intervals developed premature ventricular beats. Sosman⁶ states ventricular premature contractions occur in about half the cases when an attempt is made to pass the tip of the catheter through the tricuspid valve. Dexter³ notes that two patients developed transient auricular fibrillation which subsided spontaneously in the course of half an hour. Cournand² reports two instances of paroxysmal auricular tachycardia. Auricular premature contractions have not been reported. Cournand² states that death is known to have occurred suddenly in the case of two adult cardiacs; in neither instance was the catheterization performed with electrocardiographic control. Another death⁴ has been reported in Holland in a patient with gross disease of the coronary artery.

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DATA

Patients were routinely connected to a Viso-Cardiette and during manipulation of the catheter the stylus was observed almost continuously. At any indication of arrhythmia a recording was taken. Many yards of record were taken on each patient. Table 1 contains the data on the patients catheterized, with a notation of the arrhythmias observed. All patients are included in whom a successful catheterization was done and in whom electrocardiograms were obtained—a group of 23 patients.

Auricular premature contractions were obtained in 17 of the 23 patients. The occurrence of auricular premature contractions is not mentioned in the literature. A possible factor is that they, as shown in figure 1, do not break up the rhythm in a very noticeable manner and would be very easily overlooked. The instances in which auricular premature contractions were not found are those with only short records taken while the catheter was in the

TABLE I
Data on Cases Having Right Heart Catheterization

Patient	Age	Sex	Clinical Diagnosis	Cardiovascular Status	Arrhythmias*
M. C.	45	F	Arrested pulmonary tuberculosis. Bronchiectasis of the left lung.	Mediastinal and heart shift to the left.	V. P. C.
H. B.	49	M	Chronic pulmonary tuberculosis with cavitation in the left apex.	Radiographically a small heart.	A. P. C. V. P. C. N. P. C.
A. P.	35	F	Chronic pulmonary tuberculosis with right fibro-thorax.	Mediastinal and heart shift to the right.	No arrhythmias noted.
G. N.	47	M	Chronic pulmonary tuberculosis with marked cavitation on the left.	Mediastinal and heart shift to the left.	A. P. C. V. P. C. N. P. C.
G. J.	40	M	Chronic pulmonary tuberculosis with right thoracoplasty.	Suspected ventricular septal defect.	A. P. C. V. P. C. N. P. C.
B. H.	28	F	Chronic pulmonary tuberculosis with left extra-pleural oleo-thorax.	Normal.	Paroxysmal supra-ventricular tachycardia. A. P. C. V. P. C. Possible N. P. C.
B. S.	31	F	Chronic pulmonary tuberculosis with right pneumothorax.	Normal.	A. P. C. V. P. C.
P. A.	28	F	Chronic pulmonary tuberculosis with right thoracoplasty.	Normal.	A. P. C. V. P. C.
C. O.	27	F	Chronic pulmonary tuberculosis. Bronchial asthma.	Normal.	Marked sinus tachycardia.
E. B.	47	M	Chronic pulmonary tuberculosis with left upper lobe cavitation.	Normal.	A. P. C. V. P. C. Possible N. P. C.
D. W.	34	F	Chronic pulmonary tuberculosis with left fibro-thorax.	Mediastinal and heart shift to the left.	Paroxysmal supra-ventricular tachycardia. A. P. C. V. P. C.
E. V.	40	F	Chronic pulmonary tuberculosis with cavitation on the right.	Normal.	No arrhythmias noted on record.

* A. P. C.—Auricular premature contraction.
V. P. C.—Ventricular premature contraction.
N. P. C.—Nodal premature contraction.

TABLE I—Continued

Patient	Age	Sex	Clinical Diagnosis	Cardiovascular Status	Arrhythmias*
A. C.	29	F	Chronic pulmonary tuberculosis with marked fibrotic changes bilaterally.	Normal.	V. P. C. N. P. C. Transient partial right bundle branch block.
S. P.	21	M	Chronic pulmonary tuberculosis. Diabetes mellitus.	Normal.	A. P. C. V. P. C.
B. F.	48	F	Chronic pulmonary tuberculosis with right pneumonectomy and right thoracoplasty.	Normal.	A. P. C. V. P. C.
A. F.	23	M	Chronic pulmonary tuberculosis with cavitation on the left.	Normal.	A. P. C. V. P. C. N. P. C.
M. W.	26	F	Chronic pulmonary tuberculosis with left pneumonectomy and left thoracoplasty.	Normal.	A. P. C. V. P. C. N. P. C.
A. P.	35	F	Chronic pulmonary tuberculosis with right fibro-thorax.	Mediastinal and heart shift to the right.	V. P. C.
D. L.	39	F	Chronic pulmonary tuberculosis with right thoracoplasty and cavitation on the left.	Normal.	A. P. C. V. P. C. N. P. C.
S. B.	25	F	Chronic pulmonary tuberculosis with right pneumothorax.	Normal.	A. P. C. V. P. C.
A. P.	27	F	Chronic pulmonary tuberculosis with right thoracoplasty.	Normal.	A. P. C. V. P. C.
J. K.	36	M	Chronic pulmonary tuberculosis with right thoracoplasty.	Resolved tuberculous pericarditis.	A. P. C. V. P. C.
M. M.	41	F	Intractable asthma.	Normal.	A. P. C. V. P. C. N. P. C. Transient partial right bundle branch block.

auricle. The auricular premature contractions occurred singly, in runs of two to four from the same focus (at no great change in heart rate), and in runs from several foci.

Nodal premature contractions were noted in at least eight instances. They were seen most commonly interspersed among the ventricular premature contractions obtained as the catheter entered the right ventricle (figure 4B and 4D). In two patients auricular premature contractions occurring very early in diastole set off the phenomenon of wandering pacemaker (figure 1C). In one instance following an auricular premature contraction in very early diastole a nodal rhythm followed for 11 beats. The unusual supraventricular rhythm shown in figure 4B was obtained when the catheter was in the region of the tricuspid valve.

Supraventricular tachycardia was noted in two patients (figures 2B and 3B). One patient (B. H.) was known to have had spells of tachycardia previous to catheterization and she might have had the spell anyway or the excitement of the procedure could have brought it on. From the record it is difficult to say whether the tachycardia is auricular or nodal. In this patient it was decided to enter the right ventricle from the right auricle in spite of the tachycardia and the very unusual electrocardiogram shown in figure 2C was obtained. As the catheter entered the ventricle it set off a

run of ventricular tachycardia on whose termination the heart resumed its sinus rhythm—an unique method of stopping a paroxysmal tachycardia. In the other patient (D. W.), the occurrence of the tachycardia was discovered only several weeks after the catheterization, when, in reviewing the electrocardiogram, a strip of several inches showing the tachycardia was found (figure 3B).

Ventricular premature contractions were almost universally obtained and it is our feeling that it is a rare instance when they will not be recorded if continuous electrocardiograms are taken (figures, 2A, 2C, 3D, 4 and 7). In view of the frequency of the ventricular premature contractions it is not surprising that fusion beats were seen not infrequently. Although the ventricular premature contractions were almost always very clearly the result

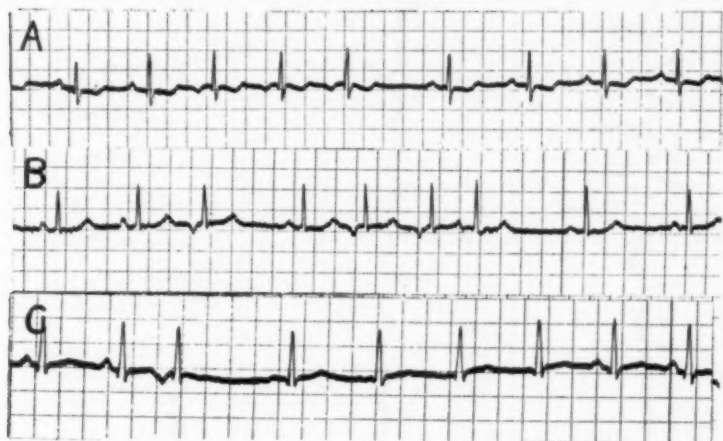


FIG. 1. A. Patient B. S. Lead II. Auricular premature contractions. B. Patient H. B. Lead III. Auricular premature contractions. C. Patient A. F. Lead II. Wandering pacemaker set off by a premature auricular contraction.

of catheter stimulation, in at least two instances a residual irritable focus remained for some time after the catheter stimulation. The occurrence of ventricular premature contractions is discussed in greater detail below.

In two patients a transient partial right bundle branch block was recorded. Patient A. C. was a 29 year old white female with a 10 year history of chronic bilateral pulmonary tuberculosis. A roentgenogram of the chest revealed marked fibrotic changes bilaterally with elevation of the right hilus. There was no clinical evidence of cardiovascular abnormality. A number 8-F catheter was used. It was passed easily into the right ventricle and the operator believes it was possibly in the pulmonary artery at the time the individual at the electrocardiograph noted the occurrence of the block (figure 5B). The catheter was immediately withdrawn, but the block

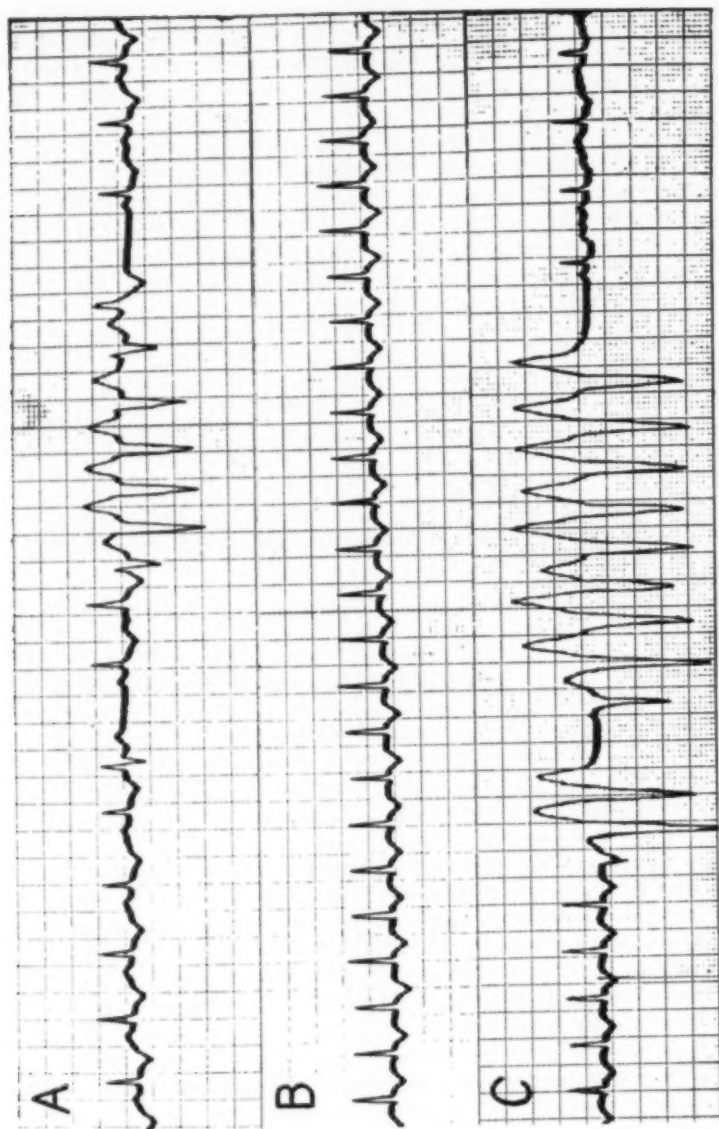


FIG. 2. Patient D. W. Lead II. A. Dominant sinus rhythm with an auricular premature contraction and a run of ventricular premature contractions. B. Paroxysmal supraventricular tachycardia. C. Paroxysmal supraventricular tachycardia followed by a run of ventricular tachycardia, set off by passing catheter through tricuspid valve, and terminating in sinus rhythm.

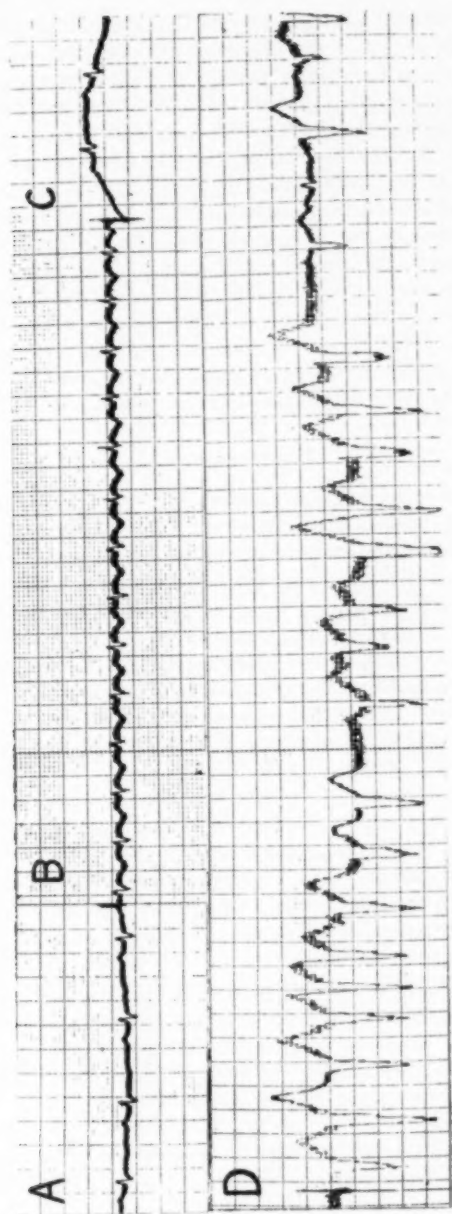


FIG. 3. Patient B. H. Lead II. A. Sinus rhythm. B. Paroxysmal supraventricular tachycardia. C. Sinus rhythm taken a short time later. D. Premature ventricular contractions occurring as catheter entered the right ventricle.

persisted. There was no change in heart rate and the patient noted no ill effects. The block persisted for about 20 minutes and disappeared completely. The electrocardiogram at various periods after the catheterization remained normal. The other patient (M. M.) was a 41 year old white female who first developed symptoms of bronchial asthma in about 1941. Since that time the patient has had progressive development of the disease with increasingly severe symptomatology. A bilateral cervico-dorsal sympathectomy was performed in February 1949. Clinical examination failed to reveal any cardiovascular abnormalities. The tip of the number 7-F catheter was moving in the direction of the apex of the right ventricle when it was suddenly flipped up into the pulmonary conus and it was at this time that the small degree of block shown in figure 6B was noted. The catheter was passed into the pulmonary artery and left in place. Electrocardiograms were taken at 5 to 10 minute intervals and the block gradually diminished in degree and was gone about 60 minutes after its onset.

DISCUSSION

The heart, like most irritable tissues, may be stimulated by different agencies—electrical, mechanical, chemical. The mechanical impact of a catheter on the cardiac musculature produces a surface-alteration which results in a rapid local decrease of surface polarization. This, if of sufficient intensity, causes stimulation. In the syncytial heart muscle, stimulation is evident as an extrasystole. Very little can be found in the literature regarding the relative sensitivity of different tissues to mechanical stimuli. This is due, on the one hand, to the difficulty of grading mechanical stimuli and on the other hand to the relative ease with which electrical stimuli can be varied and measured. Chronaxie has thus been commonly used to measure the reactivity of tissue to electrical stimuli. The chronaxie of the sinus, the auricular musculature and the ventricles has been found to be the same all over the heart.⁷ As measured by chronaxie, the excitability of the auriculo-ventricular conduction system has been found to be one-third that of the cardiac musculature. The Purkinje fibers in sheep and dogs were also found to have a chronaxie three times that of the musculature. These results with electrical stimuli do not appear to fit in with the experience of workers doing cardiac catheterizations. Ventricular extrasystoles occur most commonly just as the catheter lies in the region of the tricuspid valve, especially when the catheter is impinging on the area of the septum just beyond the valve. It is in this region that the conduction system lies. To get into the pulmonary artery the catheter in many instances impinges and scrapes against this area and ventricular extrasystoles occur in profusion. When the catheter enters the pulmonary artery the extrasystoles practically always stop. Often, as the catheter is withdrawn from the pulmonary artery, extrasystoles occur in large numbers as the tip strikes the septum just before it passes through the tricuspid valve (figure 7). If the catheter tip

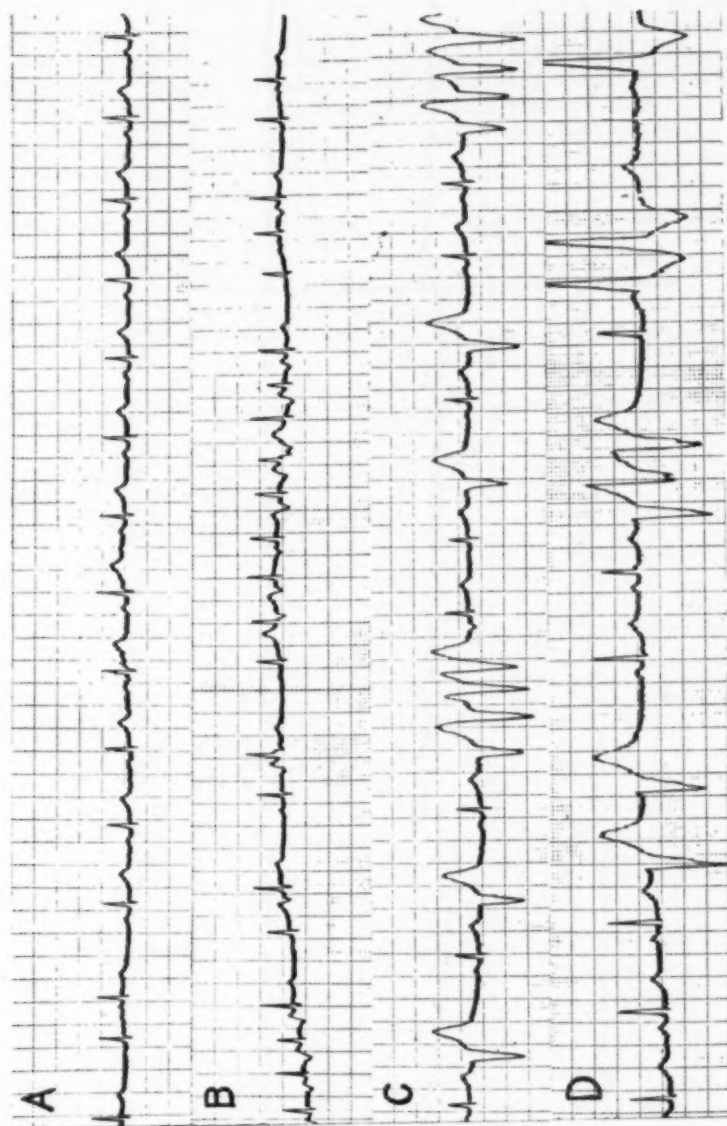


FIG. 4. Patient G. N. Lead II. A. Sinus rhythm with one auricular premature contraction. B. Unusual supraventricular arrhythmia. C. Auricular and ventricular premature contractions. D. Patient H. B. Lead II. Nodal premature contractions. Ventricular premature contractions.

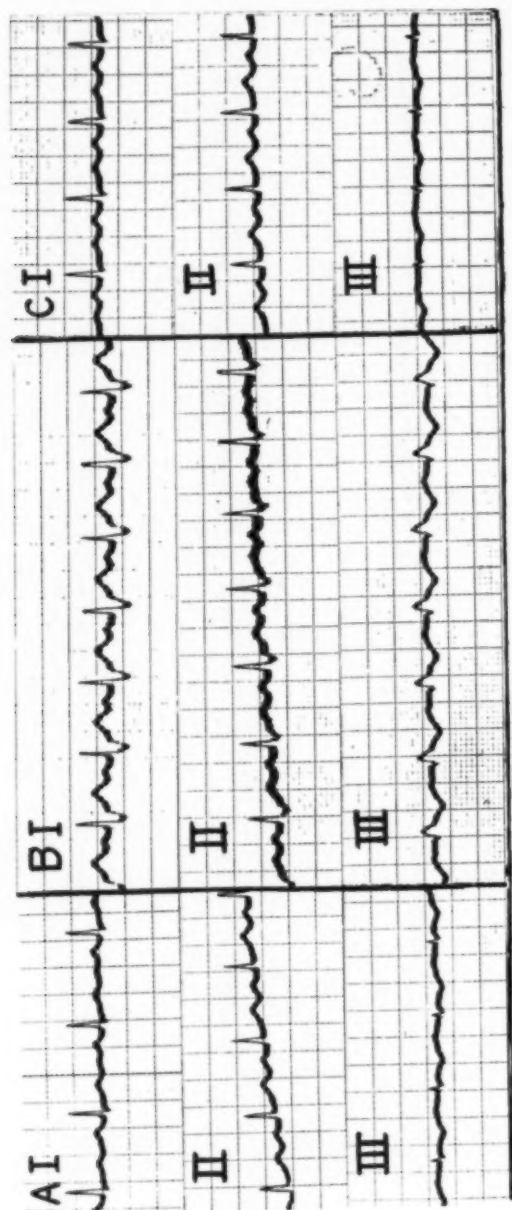


FIG. 5. Patient A. C. A. Limb leads taken before catheterization. B. Partial right bundle branch block produced during catheterization. C. Return to normal 20 minutes later.

passes down into the body of the right ventricle, extrasystoles become less frequent. These findings would indicate that the conduction system of the heart is especially sensitive to mechanical stimulation. There thus appears to be a discrepancy in the electrical and mechanical sensitivity of the conduction system. Further investigation of the problem would seem indicated. The endocardial surface of the heart and especially the septal area would appear to have a greater mechanical irritability than the epicardial surface. In cardiac surgery the surface of the heart may be sutured without too many extrasystoles. The difference may again be in the greater mechanical irritability of the conduction system—present mainly in the septal region.

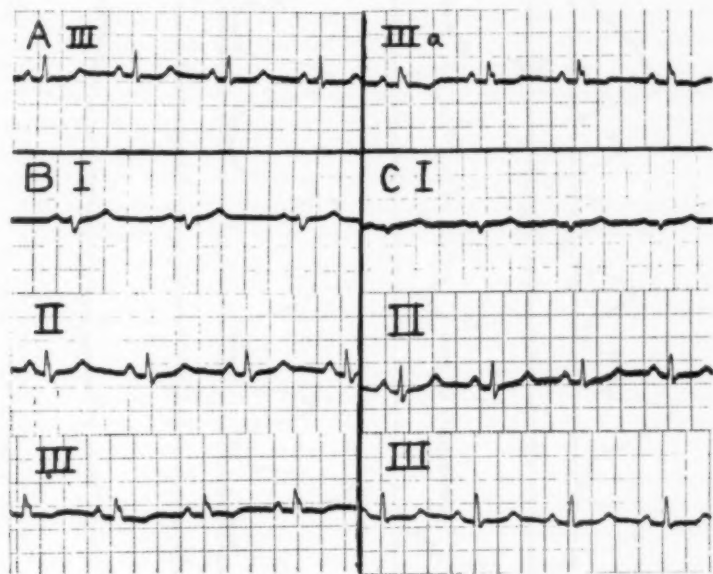


FIG. 6. Patient M. M. A. Lead III just before onset of partial right bundle branch block. A. III a. Lead III immediately after onset of block. B. Limb leads five minutes after onset of block. C. Limb leads 20 minutes after onset of block.

The extrasystoles may be single but when they are produced from the irritable area on the septum described above, they are frequently multiple. In some records the varied shape and timing of the extrasystoles would indicate multiple irritated foci (figures 4D and 7). On other occasions the uniform timing and form of the run of extrasystoles indicate a discharge from a single focus—a true run of ventricular tachycardia. It appears that a single pressure of the catheter may produce not one premature contraction but several contractions from the same focus. An ectopic pacemaker is set up. In figure 1A it would appear that the same focus discharged three times

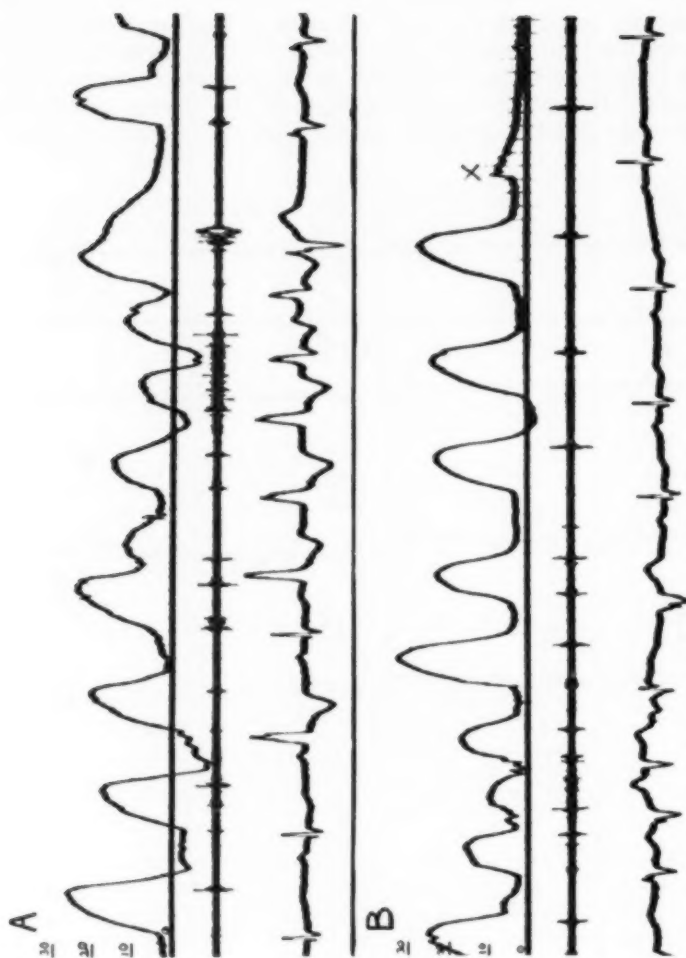


FIG. 7. Patient B. S. A. and B. are continuous records obtained while the catheter was being slowly withdrawn from the right ventricle to the right auricle. Upper record is ventricular pressure recorded through the catheter—with baseline. Middle record is heart sounds—record is spoiled by extraneous noises. Lower record is electrocardiogram. Note run of thirteen ventricular premature contractions of various forms produced just before catheter passed through tricuspid valve at X.

rather than that each premature contraction is the result of a new catheter stimulation. This is also evident in figure 2C where the run of ventricular tachycardia appears to arise from a single focus. The deformation which occurs at the edge of the compressed area can apparently persist for a short period of time and act as a continued stimulus. The pressure exerted by the tip of a number 8-F or 9-F catheter can be considerable. It is conceivable that if a region such as the A-V node, which has a strong capacity as a pacemaker, were mechanically stimulated a fairly persistent ectopic tachycardia could result.

When the tip of the catheter is in the ventricle in an area where extrasystoles are not being produced, extrasystoles will often occur when blood is being withdrawn from the catheter—suggesting that the catheter tip is against the ventricular wall and the suction produces additional deformation, resulting in stimulation.

Although a heart subjected as a whole to a uniform pressure can withstand high pressures with no effect on conduction or actual improvement in conduction, relatively slight pressure on a nerve can stop conduction when applied locally. The pressure stops conduction by producing deformation and displacement of material. The deformation that occurs at the edges of the compressed region must involve a displacement of liquid substance of the tissue system and some tissue injury through rupturing the fiber elements.⁶ Since the right bundle branch is in a region where the catheter might impinge upon it, it is almost to be expected that in a certain percentage of catheterized patients a right bundle branch block might be produced. Since it can be recognized only by routine electrocardiography, its failure of being reported could only mean that routine electrocardiograms are not being as extensively used as they should be. Even taking an electrocardiogram before and after the catheterization as is being practiced by some groups would not pick up all instances of bundle branch block because, as in the cases reported, it may be quite transient and be gone before the catheterization is completed. It is conceivable but possibly unlikely that a permanent right bundle branch block could result from a cardiac catheterization. It also appears evident that the pressure of the catheter on the endocardium cannot be considered as having no detrimental effect, and the heavier the catheter, the more rigid the catheter (as with the use of a metallic stylus), the more danger of damage.

Where catheterization is done in damaged hearts the danger of death from arrhythmia is greatly increased. When the heart is depressed by organic disease, not only is the refractory phase of the muscle increased but, due to the focal areas of damage, the refractory periods of adjacent areas may be very unequal; as a result the conditions are ideal for the production of ventricular fibrillation by a premature impulse initiated by the catheter tip. A slowly moving impulse set off during the early relative refractory phase would be blocked from some areas due to the prolonged refractory

period of these damaged areas, but somewhat later might be able to gain access to these unstimulated areas from another direction. By this time the areas first stimulated may have passed through the refractory phase and would be again stimulated—the phenomenon of reentry. Continuous multiple reentries from several points could result in ventricular fibrillation.⁹ It has been shown that late systole constitutes a vulnerable period during which a single shock delivered to a localized region of the ventricle can produce ventricular fibrillation.¹⁰ By catheter it is possible to get stimulation at any phase in the cycle and the danger of production of ventricular fibrillation would seem to be real.

The low incidence of fatalities in cardiac catheterization speaks highly for the ability of the heart to withstand mechanical stimulation—often of severe degree. Catheterization is so valuable a research tool that it is important to keep the mortality rate at the lowest possible figure to avoid putting the procedure in disrepute. As more people, with little experience, undertake the procedure, it is possible that the number of fatalities may rise. It is therefore important that every precaution possible be taken to avoid mishap. Certainly the taking of electrocardiograms routinely during the catheterization is valuable—if for no other reason than to familiarize the operator with the number and degree of arrhythmias which he can produce with the procedure. If the catheterization is being monitored by electrocardiographic observation, it is possible to withdraw the catheter when the arrhythmias become alarming. On the other hand it is also true that often one must push past the area giving the arrhythmias to get the catheter into the pulmonary artery. The safest place for the catheter tip is in the pulmonary artery. If the catheter must be left in place any length of time and especially if the patient is to be exercised or moved, the catheter should if possible be passed to the pulmonary artery. If it must be left in the right ventricle, it would seem imperative to have a continuous electrocardiographic control of the procedure. If displaced, it might impinge on the septal area and produce dangerous unrecognized arrhythmias. An instance of death during catheterization is believed to have resulted from displacement of the catheter from the pulmonary artery to the right ventricle during exercise.¹¹

Some preliminary work indicates that quinidine and procaine might be of value in inhibiting the arrhythmias. In most instances, however, where catheterization is done some problem is under investigation and the actions of these drugs would complicate and confuse the results.

SUMMARY

The arrhythmias encountered in a group of 23 patients in whom right heart catheterization was done with close electrocardiographic supervision are described.

1. Auricular premature contractions were noted in 17 patients.
2. Nodal premature contractions were noted in at least eight patients.

3. Ventricular premature contractions were noted in 20 patients.
4. Paroxysmal supraventricular tachycardia occurred in two patients.
5. Transient partial right bundle branch block occurred in two patients.

The mechanism of production of these arrhythmias and their importance are discussed.

ADDENDUM

Since this article was submitted for publication we have encountered three additional cases of transient partial right bundle branch block in a group of thirty cases who were catheterized. In two of these cases, the block persisted for three and six hours respectively, while in the third case the block was observed for a period of 90 seconds during which time the electrocardiogram was being continually observed.

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THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE (A POSTMORTEM COR- RELATION STUDY OF 53 CASES) *

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RECENTLY there has been a renewed interest in congenital heart disease. The use of chamber catheterization,^{1, 2} angiocardiology^{3, 4, 5, 6, 7, 8} and the establishment of definitive fluoroscopic criteria by Taussig⁹ have added considerably to our fundamental knowledge of this field. Surgical technics have been perfected for the successful treatment of patent ductus arteriosus,¹⁰ coarctation of the aorta,^{11, 12} and some lesions associated with pulmonary stenosis or atresia as the tetralogy of Fallot, non-functioning right ventricle, and truncus arteriosus communis.^{13, 14}

It was felt in view of these developments that a review of the electrocardiographic aspects might be useful. This study is an attempt to reevaluate the electrocardiographic findings of congenital heart disease, so that if possible, there may be a better understanding of the significance or limitations of this phase of cardiology.

Correlative postmortem and electrocardiographic studies, with the exception of isolated case reports, are relatively rare. The outstanding monograph of Schnitker¹⁵ is the most extensive study to this date. His work contained 106 cases, all the available instances of combined reports between 1915 and 1940, when the work was published.

DISCUSSION OF RESULTS

The series here presented was formulated by a review of all cases of congenital heart disease found on postmortem examination at the Michael Reese Hospital between the years 1920 and 1948. A total of 53 of these necropsied cases had had electrocardiograms and were selected for study. A brief description of the pathological and electrocardiographic findings and pertinent comments are presented in table 1. The electrocardiograms, usually only the limb leads, are reproduced in figure 1. Reference will be made to suitable sources in the literature for these types of lesions for which there were no electrocardiograms in the present series. The cases encountered are listed in table 2.

The existing clinical and pathological classifications of congenital heart disease cannot be used as a grouping basis for an electrocardiographic classification. Schnitker¹⁵ separated his cases according to Maude Abbott, into

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TABLE I
Cases and Findings

Cases	Age	Pathologic Findings	ECG	Comments
I. Cor triloculare biatriatum				
1. S. M.	40 days	Hypertrophied single ventricle; transposition of aorta and pulmonary artery; patent foramen ovale; marked hypertrophy of rt. auricle; no communication between rt. auricle and rt. ventricle; pulsion diverticulum into lt. auricle. Tricuspid valve atresia.	Left heart strain	Cases 1 and 2 show left heart strain pattern. Case 3 is interesting. It shows at the time of first record a left axis shift, abnormal at this age. The electrocardiogram three years later shows the development of a severe left heart strain pattern. Case 4 does not conform with the pattern proposed for this lesion.
2. B. G.	4½ mos.	Tricuspid valve atresia; patent foramen ovale and septum primum; hypoplasia rt. ventricle; patent interventricular septal defect.	Possible left heart strain (tendency to low voltage)	
3. D. T.	4 yrs.	Single ventricle with persistent A-V communis; A-V valve has 5 leaflets; both auricles connect with ventricle; stenosis of pulmonary conus; patent foramen ovale, 1 cm.; heart wt. 150 gm.	Left heart strain	
4. B. P.	Newborn	Tricuspid valve fused, slit-like; heart enlarged; rt. auricle markedly hypertrophied and dilated; rt. ventricle very small; pulmonary conus thick walled; no communication between rt. ventricle and pulmonary artery; pulmonary valve tricuspid, all cusps fused; wide patent ductus arteriosus; lt. auricle and lt. ventricle dilated; patent foramen ovale 1.1 by 1.0 cm.	Possible right heart strain	

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
II. Cor triloculare biventriculare				
5. I. S.	3 mos.	Absent interauricular septum; transposition of great vessels; rt. ventricle hypertrophied; heart borders 2.5 cm. to left of sternum, and 3.5 cm. to rt. of sternum.	K-W* Combined heart strain	This case might be included with the group of transposition of the great vessels; it shows the Katz-Wachtel phenomenon and combined heart strain. Note further that all of the components in Leads I and II are inverted, yet this is not a case of dextrocardia, but is a dextroverso cordis, for the heart was almost entirely to the right of the sternum.
III. Auricular septal defect, or foramen ovale defect, 1 cm. or greater				
6. B. H.	4 days	General cardiac enlargement; patent foramen ovale 1 cm.; patent ductus arteriosus.	Low voltage	Dynamically significant auricular septal defects usually produce right heart strain ^a if not complicated by associated disease processes, i.e., degenerative changes, hypertension, etc. However, mitral stenosis accentuates the tendency to right heart strain. In this series, a variety of electrocardiograms is noted. Viewing the individual cases, it is obvious that age and associated pathologic disturbances are the factors which determine the ultimate electrocardiographic manifestations.
7. N. L.	3 mos.	Heart enlarged, wt. 25 gm.; rt. ventricle enlarged; widely patent foramen primum, 1.2 cm.	K-W*	
8. B. B.	20 mos.	Rt. auricle and rt. ventricle markedly dilated; patent foramen ovale 1.2 cm.	Right axis shift	
9. L. F.	19 yrs.	Interauricular septal defect 4×3 cm.; marked hypertrophy and dilation of rt. auricle and ventricle; aorta hypoplastic; lt. auricle and ventricle normal; rheumatic endocarditis of mitral and aortic valves and on edge of septal defect.	Intraventricular block, indeterminate type	
10. W. Y.	51 yrs.	Interauricular septal defect, admits "2 fingers"; marked dilation and hypertrophy of rt. auricle and ventricle; lt. auricle and ventricle normal.	S type of intraventricular block	
11. F. P.	57 yrs.	Patent foramen ovale 1.5 cm.; rt. auricle and ventricle dilated; lt. ventricle slightly hypertrophied; arteriosclerotic thickening mitral valve; arteriosclerotic plaques in coronary arteries and ascending aorta.	Left axis shift; abnormal P waves	

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
12. J. R.	70 yrs.	Patent foramen ovale 1 cm.; moderate enlargement left ventricle; all coronary arteries have subintimal thickening and arteriosclerotic plaques; lt. circumflex narrow throughout; aortic valve has many fenestrations.	Left heart strain; auricular fibrillation	
IV. "Biloculate" heart				
13. B. S.	Newborn	Atresia of the aorta with defective development of left ventricle and atresia of mitral ring; rt. auricle dilated; rt. ventricle very large; pulmonary conus and pulmonary artery enlarged; wide patent ductus arteriosus.	1st degree A-V block Intraventricular block, uncommon type.	No specific conclusions can be drawn from the electrocardiogram in these 5 cases.
14. B. R.	9 days	Anomaly of venous return; sup. and inf. venae cavae and pulmonary veins empty into common auricle; small remnant of auricular septum noted; rt. ventricle large; hypoplasia of lt. ventricle; mitral atresia; truncus solitarius.	Rt. axis shift, possible rt. heart strain.	
15. J. H.	10 days	Wt. 24 gm.; atresia of the aorta with defective development of the lt. ventricle and atresia of mitral ring; large rt. auricle and rt. ventricle; dilated pulmonary artery.	Normal ECG (no axis shift)	
16. D. C.	6 mos.	Anomaly of venous return sup. and inf. venae cavae and pulmonary veins empty into rt. auricle; very large rt. auricle and ventricle; very small lt. ventricle with hypoplasia of lt. auricle.	K-W*	
17. M. H.	7 yrs.	Atresia of the aorta with defective development of the left ventricle and atresia of the mitral ring; heart wt. 200 gm.; marked enlargement of the rt. ventricle; prominent pulmonary conus; patent ductus arteriosus; inter-ventricular septal defect 1 cm.; enlarged left auricle.	12/24/35 Rt. axis shift, possible rt. heart strain 4/14/36 K-W? Combined heart strain	

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
V. Transposition of the great vessels				
18. B. S.	Newborn	Transposition of great vessels; heart grossly enlarged, especially rt. auricle and ventricle; coarctation of aorta; patent foramen ovale, 2.5 cm.; wide patent ductus arteriosus; no interventricular septal defect.	Right heart strain (note narrow QRS complexes)	It is interesting that of 5 cases of transposition of the great vessels, 3 showed the Katz-Wachtel phenomenon. In fact, if one were to include the case of cor triloculare biventriculare (Case 5), it could be stated that 4 of the 6 cases of transposition in this series showed this pattern. Although, as indicated, a variety of lesions present this electrocardiographic pattern, it seems to occur in highest incidence in cases of transposition.
19. B. W.	7 days	Heart slightly enlarged; transposition of great vessels; wide patent foramen ovale and patent ductus arteriosus; no interventricular septal defect; rt. ventricle thickened.	Right heart strain (note narrow QRS complexes)	
20. D. D.	1 mo.	Heart distinctly enlarged; transposition of great vessels; overriding aorta; coarctation of aorta; patent foramen ovale less than 1 cm.; interventricular septal defect 0.5 to 1.0 cm.; wide patent ductus arteriosus; hypoplasia rt. auricle; large rt. ventricle; hypertrophy and dilation of lt. auricle; lt. ventricle normal; presence of "muscle bundle of lt. ventricle"; fusion of crista supraventricularis with ventricular septum.	K-W* Combined heart strain	
21. E. F.	2 mos.	Heart enlarged; transposition of great vessels; wide patent ductus arteriosus and foramen ovale; no interventricular septal defect.	K-W*	
22. D. F.	4½ mos.	Transposition of great vessels; absent septum primum (2.5 cm.); one continuous valve across mitral and tricuspid areas; overriding aorta; very large rt. auricle and ventricle.	Left heart strain Possible K-W*	
VI. Coarctation of the aorta (adult type)				
23. B. C.	3 mos.	Coarctation of aorta; heart enlarged; both auricles increased in size; rt. and lt. ventricles dilated and hypertrophied.	Possible combined heart strain	One of the cases showed the Katz-Wachtel phenomenon. Left heart strain pattern was not found.

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
24. J. J.	6 mos.	Coarctation of aorta; markedly enlarged left ventricle; pulmonary artery and ductus arteriosus widely patent; small interventricular septal defect (2 mm.).	K-W*	
25. M. G.	47 yrs.	Coarctation of aorta; rt. and left ventricular hypertrophy, the heart not enlarged. Death caused by dissecting aneurysm.	Left axis shift (Record taken at age 42)	
VII. Congenital stenosis of isthmus of aorta				
26. H. R.	47 yrs.	Congenital stenosis of isthmus of aorta; marked hypertrophy and dilatation of lt. ventricle; rt. ventricle hypertrophied; early media necrosis (Erdheim) of ascending aorta.	Chronic coronary insufficiency	A chronic coronary insufficiency, probably the result of long standing hypertension.
VIII. Patent ductus arteriosus				
27. B. S.	25 days	Heart markedly enlarged, wt. 35 gm.; rt. ventricle very large; bicuspid pulmonic valve; dilated pulmonary artery; very wide patent ductus arteriosus; aortic orifice markedly narrowed; aortic valve a single cusp; mitral valve small and bicuspid.	Possible combined heart strain	
28. C. B.	23 yrs.	Heart wt. 350 gm.; patent ductus arteriosus; rheumatic mitral and aortic endocarditis, with superimposed subacute bacterial endocarditis.	Left axis shift	
29. A. B.	33 yrs.	Heart wt. 300 gm.; patent ductus arteriosus; slight enlargement of auricles and ventricles.	Left axis shift Abnormal record	
IX. Right sided aortic arch				
30. D. C.	6 yrs.	Heart wt. 100 gm.; rt. sided aortic arch; slight cardiac hypertrophy and dilation.	Right heart strain	The characteristic right heart strain pattern is found.

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
X. Von Gierke's disease				
31. I. M.	6 wks.	Heart tremendously enlarged; wt. 100 gm.; widely patent ductus arteriosus.	Combined heart strain	The cases show the expected combined heart strain pattern.
32. P. B.	3 mos.	Heart markedly enlarged, wt. 160 gm.; right and left ventricles dilated and hypertrophied.	K-W* Combined heart strain	
XI. Isolated interventricular septal defects				
33. E. T.	3½ yrs.	Heart slightly enlarged; wt. 115 gm. (size of defect not given); tricuspid bacterial endocarditis.	Right axis shift	The electrocardiogram is non-contributory in septal defect cases, though frequent reference in literature to the occasional presence of intraventricular conduction defects is acknowledged.
34. V. M.	12 yrs.	Heart slightly enlarged, wt. 150 gm.; 3 mm. septal defect; endocardium hyalinized and thickened; tricuspid bacterial endocarditis.	Left axis shift	
35. E. M.	38 yrs.	Heart enlarged, wt. 400 gm.; 8 mm. defect lower portion of septum; old mitral endocarditis; moderate coronary sclerosis.	Left axis shift	
XII. Defects of pulmonary conus or artery				
36. C. M.	14 yrs.	Heart wt. 175 gm.; congenital adhesive band of rt. posterior cusp to pulmonary artery, 0.2 cm. from normal commissure; numerous intimal atheromatous deposits in coronary artery.	Right axis shift	The electrocardiogram is non-contributory.
37. B. J.	35 yrs.	Heart enlarged, wt. 450 gm.; rt. auricle and rt. ventricle hypertrophied; pulmonary conus dilated; it is separated from the rt. ventricle by a firm fibrous band; orifice between the two is 1 cm. in diameter; pulmonary conus filled with large friable vegetation, also noted on pulmonary artery and valve; interventricular septal defect 0.15 cm., with vegetation attached.	(When 24 yrs. old) normal record	

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
XIII. Non-classifiable case				
38. B. B.	2 mos.	Heart pale brown and soft; no abnormalities noted.	Low voltage, narrow QRS complexes	This case was described as showing no abnormalities at necropsy, yet the abnormal electrocardiogram is possibly suggestive of the existence of an anomalous origin of the left coronary artery from the pulmonary artery. Since the syndrome was not reported in the literature until several years after this case came to post mortem, this diagnosis is possible.
XIV. Congenital bicuspid aortic valve				
39. R. K. ⁴	11 yrs.	Wt. 330 gm.; bicuspid aortic valve; old rheumatic mitral and aortic endocarditis.	(Moribund record not shown)	All these cases, with the exception of one (Case 39) were found in the ages between 32 and 82. The question as to whether these were congenital bicuspid lesions, or were congenital with superimposed rheumatic endocarditis, or whether these were simply normal aortic valves which had been involved by rheumatic infection, is a factor to be considered, but will not be discussed here. Calcific changes of the aortic valve were found in 7 cases, and acute and subacute bacterial endocarditis were found in 4 cases. The prevalence of degenerative vascular disease and hypertension in addition to the stenotic aortic valvular lesions account for the high incidence of left heart strain pattern in this group.
40. M. T.	32 yrs.	Wt. 460 gm.; incomplete division of cusps of aortic valve; old rheumatic endocarditis of aortic, mitral and pulmonary valves; calcification and subacute bacterial endocarditis of aortic valve.	Left heart strain	
41. W. B.	41 yrs.	Bicuspid aortic valve; old rheumatic and acute bacterial endocarditis of aortic and mitral valves.	Intraventricular block, common type	
42. R. M.	41 yrs.	Bicuspid aortic valve; old rheumatic and severe acute bacterial endocarditis of the mitral and aortic valve.	Chronic coronary insufficiency	
43. J. G.	42 yrs.	Wt. 1000 gm.; bicuspid aortic valve; old rheumatic endocarditis of mitral and aortic valves with calcification; tuberculous pericarditis with severe calcification, up to 2 cm. in thickness.	Severe left heart strain (note P waves suggestive of P mitrale)	
44. I. J. K.	48 yrs.	Wt. 400 gm.; left ventricular hypertrophy and dilatation; bicuspid aortic valve; chronic myocarditis.	1st degree A-V block; intraventricular block, common type	

TABLE I—Continued

Cases	Age	Pathologic Findings	ECG	Comments
45. A. N.	49 yrs.	Wt. 500 gm.; bicuspid aortic valve; aortitis with insufficiency; healed endocarditis of mitral and aortic valves; atherosclerosis, rt. and left coronary arteries, esp. left; myocardium, left ventricle posterior wall, is thin and fibrotic.	Chronic coronary insufficiency posterior wall type	
46. S. G.	51 yrs.	Wt. 425 gm.; bicuspid aortic valve; old rheumatic endocarditis, mitral and aortic valves; subacute bacterial endocarditis mitral and aortic valves; syphilitic aortitis.	Left axis shift	
47. L. B.	56 yrs.	Wt. 250 gm.; bicuspid aortic valve with calcification.	Chronic coronary insufficiency	
48. C. K.	58 yrs.	Hypertrophy and dilatation of all chambers; bicuspid aortic valve with stenosis and calcification; Mönckeberg sclerosis of coronary arteries.	Left heart strain	
49. D. C.	62 yrs.	Wt. 575 gm.; bicuspid aortic valve with severe stenosis and calcification; rheumatic mitral endocarditis, old.	Left heart strain; (note P waves); digitalis S-T-T contour	
50. L. C.	62 yrs.	Wt. 480 gm.; bicuspid aortic valve; old and recent rheumatic endocarditis, mitral and aortic valves.	Normal record	
51. E. K.	64 yrs.	Wt. 375 gm.; bicuspid aortic valve with calcification; generalized atheromatosis.	Normal record	
52. W. L.	68 yrs.	Wt. 525 gm.; bicuspid aortic valve; general atheromatosis.	Left heart strain	
53. R. S.	82 yrs.	Wt. 400 gm.; bicuspid aortic valve; with extensive calcification; arteriosclerosis.	Chronic coronary insufficiency	

* K-W, Katz-Wachtel phenomenon (see text).

cyanotic, acyanotic and late cyanotic groups. No electrocardiographic correlations could be established.

Perusal of the literature and a review of our cases suggest that congenital lesions can be divided into two groups by the electrocardiographic patterns they produce. These patterns are designated as "specific" and "non-specific." Both are pathognomonic for the existence of congenital heart disease in infancy and early childhood, the former indicating particular lesions, the latter indicating the presence of congenital anomalies, the nature of which is indeterminate from the electrocardiogram alone.

Necessary to this concept is the electrocardiographic distinction between "axis shift" and "heart strain," the definitive criteria for which have been well established.¹⁶ The importance of this distinction is emphasized because

TABLE II

Cor triloculare biatriatum	
Tricuspid atresia	3
Single ventricle	1
Cor triloculare biventriculare with transposition of the great vessels	1
Auricular septal defect, or, patent foramen ovale (isolated lesion) (1.0 cm. or greater)	7
Functional biloculate heart (aortic atresia)	3
(Anomalous venous drainage; superior and inferior venae cavae and pulmonary veins into right auricle)	2
Transposition of the great vessel	
with ventricular septal defect	2
without ventricular septal defect	3
Coarctation of the aorta, adult type	3
Congenital stenosis of the isthmus of the aorta	1
Isolated patent ductus arteriosus	3
Isolated ventricular septal defect	3
Von Gierke's disease	2
Right sided aortic arch	1
Congenital defect of the pulmonary conus or artery	2
"Congenital" bicuspid aortic valve	15
Non-classifiable	1
Total	53

it was found that, in some instances, specific congenital lesions may be suggested by the strain pattern produced. Standard texts of electrocardiography should be consulted for the characteristics of the electrocardiogram in infancy and childhood.^{15, 16} This is essential for the proper evaluation of electrocardiograms in congenital heart disease.

It must be emphasized that the classification presented in this report decreases greatly in value beyond the period of infancy and childhood. The fairly widespread incidence of rheumatic endocarditis, either per se, or engrafted on congenital lesions, will alter the electrocardiographic findings. The great variety of lesions affecting the cardiovascular apparatus, many of extracardiac origin, such as hypertension, nephritis, degenerative vascular changes, and some pulmonary conditions, likewise will alter the electrocardiogram.

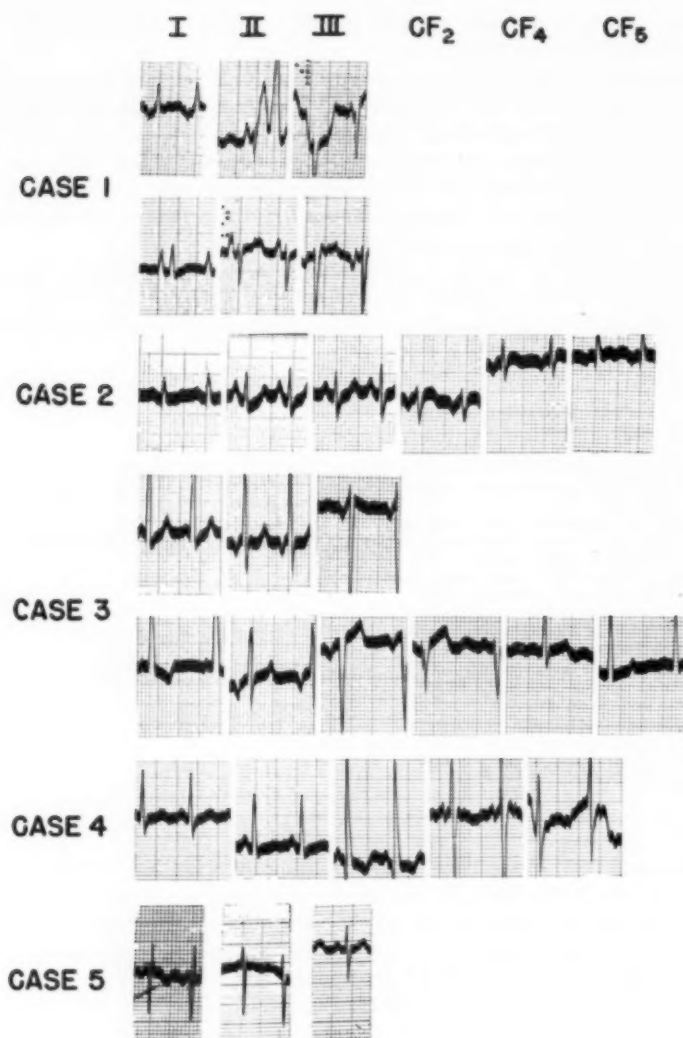


FIG. 1.

Some of the lesions in the "specific pattern" group may be found at post mortem, in cases whose electrocardiograms had not shown the proposed patterns. The variety of aberrations even in a lesion described as a single entity, will rarely produce two hearts that are completely identical

from a cardiodynamic as well as anatomic standpoint. Disturbances of impulse conduction and summation in a given heart may be beyond explanation at the present time. No other reasons can be offered for the finding of a normal electrocardiogram in the presence of some of the profoundly altered hearts that are seen.

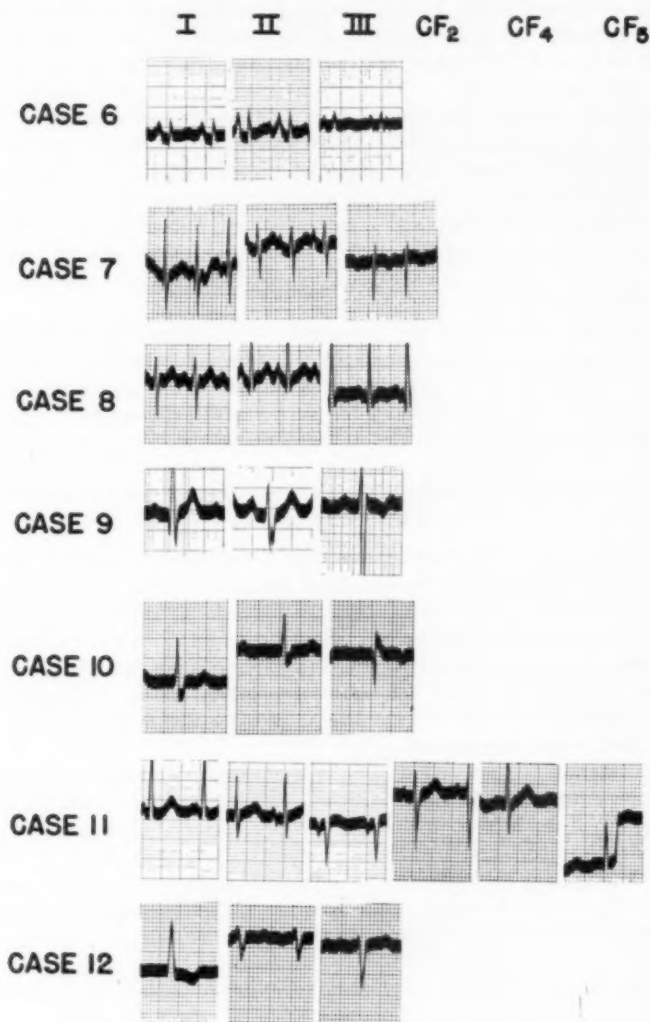


FIG. 2.

A. "*Specific*" Patterns. This group is comprised of several congenital lesions which may be suspected almost unequivocally from the electrocardiogram alone. These lesions are enumerated and described below:

I. *Dextrocardia*

This condition is the easiest congenital anomaly to recognize electrocardiographically because of the classical total inversion of all the components in Lead I. (Reversal of the two arm electrodes in this lead may produce the same findings.) Though this study has no such case which has come to post mortem, the picture is a well recognized one. The proper reading of the standard limb leads is obtained when Lead I is mirrored, i.e., the complexes are viewed with all the deflections upright, and Leads II and III are interchanged. It should be noted that, if the patient survives to adult life, and there be superimposed heart strain or myocardial infarction, the QRS and T wave changes due to these associated lesions will be found.^{17, 18} About one-third of the cases of isolated dextrocardia are associated with other congenital lesions.

It has been pointed out that there may be displacement of the heart to the right by a variety of pulmonary and thoracic abnormalities (dextroversio cordis). Inversion of P_1 may be noted in such cases, and careful clinical evaluation is necessary to avoid calling such cases dextrocardia.¹⁹ Inversion of P_1 and P_2 may be seen in cases of large single auricle (Case 5).

II. *Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery*

Multiple types of anomalous coronary disposition are known to occur, but the most significant is the origin of the left coronary artery from the pulmonary artery. Analysis of 21 cases by Soloff²⁰ revealed that the left coronary artery arose from the pulmonary artery in 17 cases, the right from the pulmonary artery in two cases, and in two cases both left and right coronaries originated from the pulmonary artery. Clinically, these cases suffered repeated episodes of cardiac failure usually terminating in death by the third to the fifth month.

The diagnosis of anomalous origin of the left coronary artery from the pulmonary artery may be made with reasonable certainty, when the electrocardiogram of an infant, in the age group mentioned, presents the picture of anterior wall coronary insufficiency or myocardial infarction.²¹ There is usually low voltage in the limb leads and abnormally elevated S-T₁ and possibly S-T₂, with inverted T₁ and possibly T₂ of coronary configuration. The chest leads usually resemble those found in adult anterior wall infarction.

III. *Von Gierke's Disease, and Possibly Congenital Idiopathic Hypertrophy*

Von Gierke's disease, or glycogen storage disease, is known to affect the heart as well as the liver and kidneys. In spite of the fact that this is a

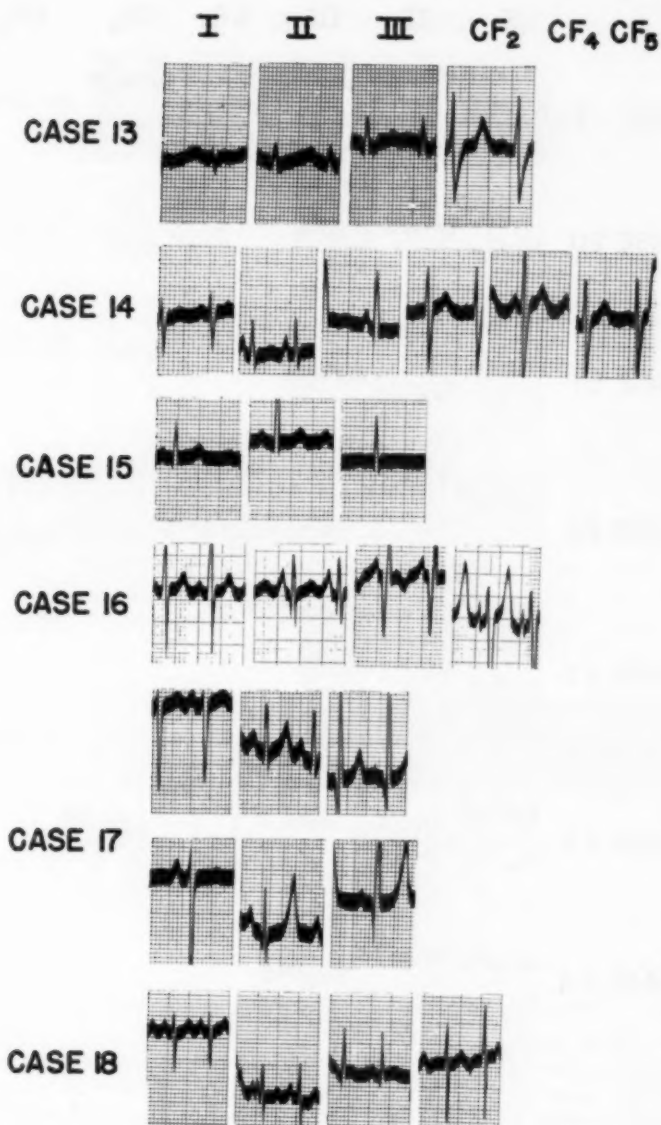


FIG. 3.

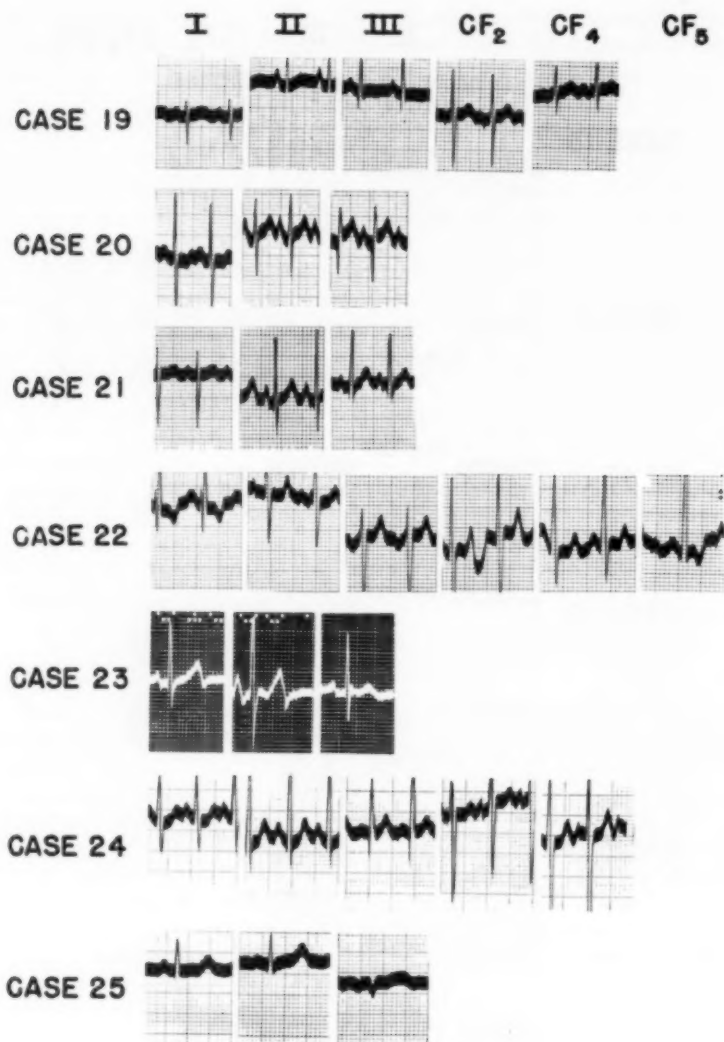


FIG. 4.

metabolic disease, its presence produces profound cardiac changes which are manifest almost from birth. Death usually occurs within three months.

Congenital idiopathic hypertrophy is a term that should be used when there is primary hypertrophy or hyperplasia of the muscle fibers without sig-

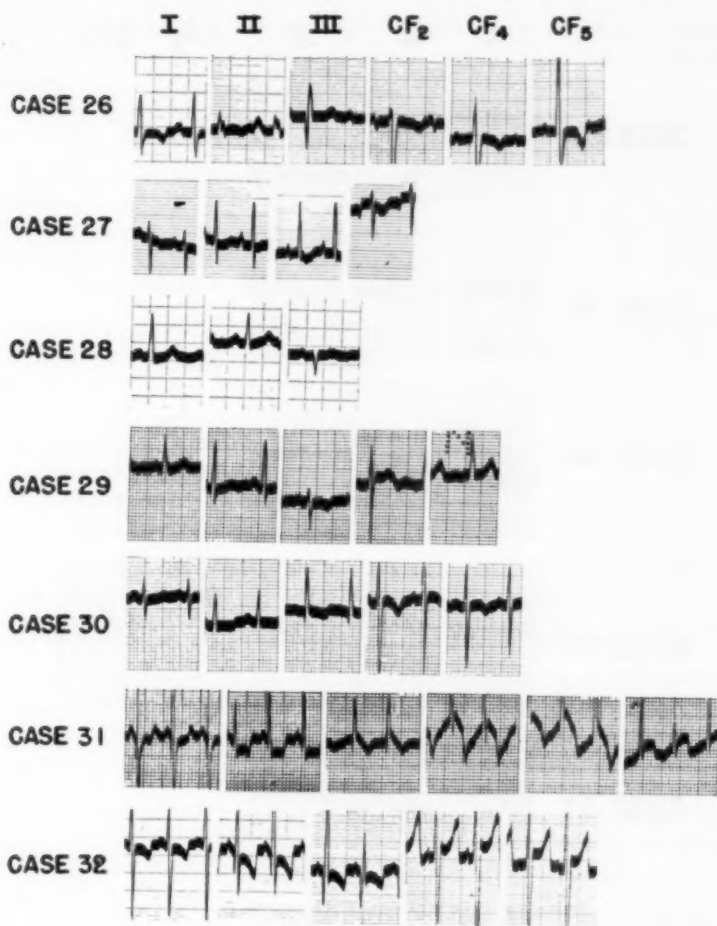


FIG. 5.

nificant cellular infiltration or fibrosis according to Schnitker.¹⁰ There should be no detectable abnormalities in the intrinsic or great vessels or no valvular or other structural deformities of the heart. Obviously, also, there should be no extracardiac etiologic factors such as severe anemia, renal disease or hypertension.

Electrocardiographically, as would be expected in the presence of diffuse involvement of the total muscular structure of the heart, there should be evidence of combined heart strain. Case 31 of this series is a classical ex-

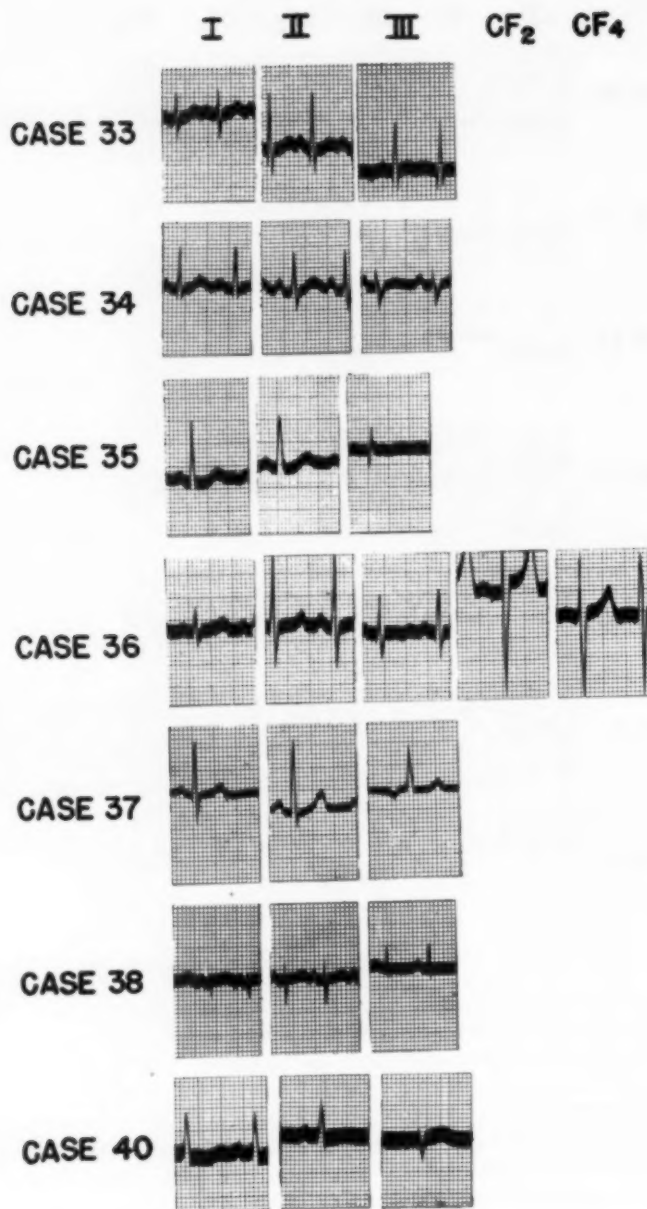


FIG. 6.

ample. (For diagnostic criteria of combined heart strain, refer to Katz.¹⁸) There is a striking resemblance between this case and Case 11a of Schnitker's series.

IV. *The Meaning of Left Heart Strain Pattern in Infancy*

Left heart strain is present in a group of cardiac anomalies, which is distinctive electrocardiographically. It is a very small group, in contrast to the great number of abnormalities which manifest right heart strain patterns, hence is of considerable importance. The lesions in this group are subdivided as follows:

A. Lesions affecting the systemic outflow tract and aorta, except for the syndrome produced by aortic atresia with underdeveloped left ventricle. They consist of:

1. Subaortic and aortic stenosis.
2. Possibly bicuspid aortic valve because of the frequent involvement by endocarditic lesions.
3. Coarctation of the aorta (adult type).
4. Congenital stenosis of the isthmus of the aorta.

(Obviously, in this group the primary stress is on the left ventricle, and electrocardiographic evidence will usually so indicate.)

B. Lesions in which there is an anomaly of the tricuspid valve.

1. Defective development of the right ventricle associated with congenital tricuspid atresia. (Usually also with atrial or ventricular septal defects, patent ductus arteriosus, and pulmonary atresia, or, at times, with transposition of the great vessels.)
2. "Ebstein's disease"—congenital downward displacement of the tricuspid valve, usually unassociated with other anomalies. (The frequent disturbances of intraventricular conduction are pointed out by Taussig.⁹)

C. Truncus arteriosus communis—a condition in which a single great vessel receives blood from both ventricles. This vessel most commonly overrides a ventricular septal defect. The lungs are supplied either by pulmonary arteries arising from the base of the great vessel, or via the bronchial arteries.

D. Single ventricle—This condition may be associated with truncus arteriosus, or may occur with both great vessels arising from a rudimentary chamber; or arising normally (cor triloculare biatriatum); or with absence of an auricular septum (cor biloculare).

Left heart strain pattern may be seen in all of the above lesions.

E. "*Non-Specific*" Patterns. The term "non-specific" pattern is here used to denote the electrocardiographic finding of some abnormality that is

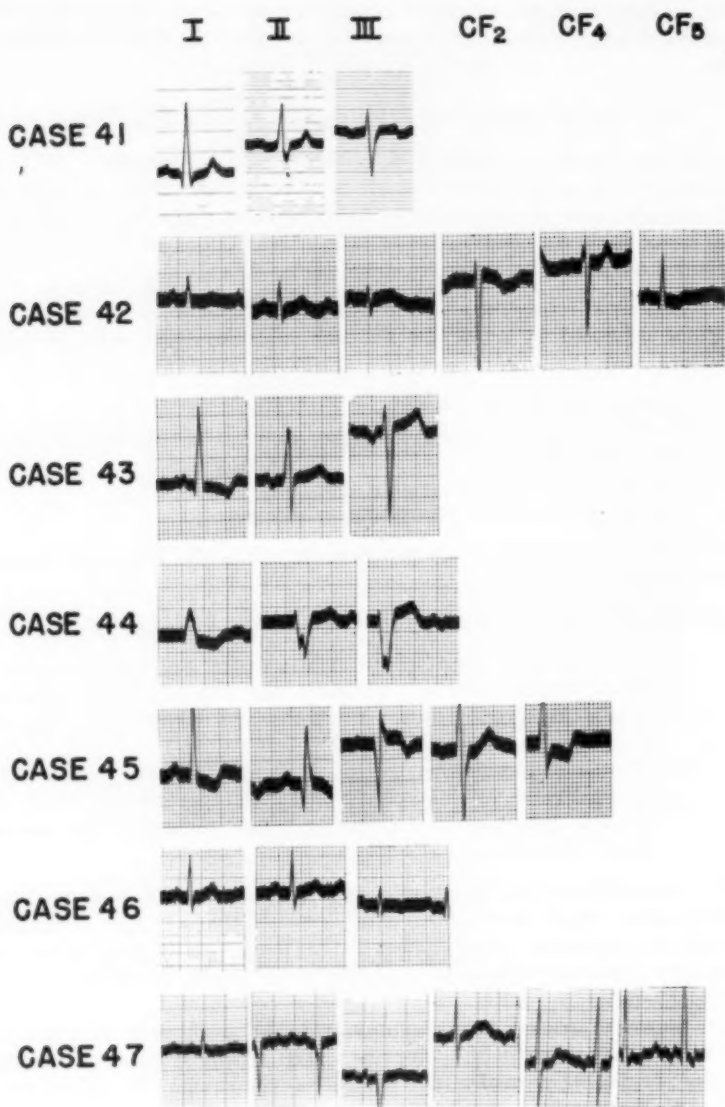


FIG. 7.

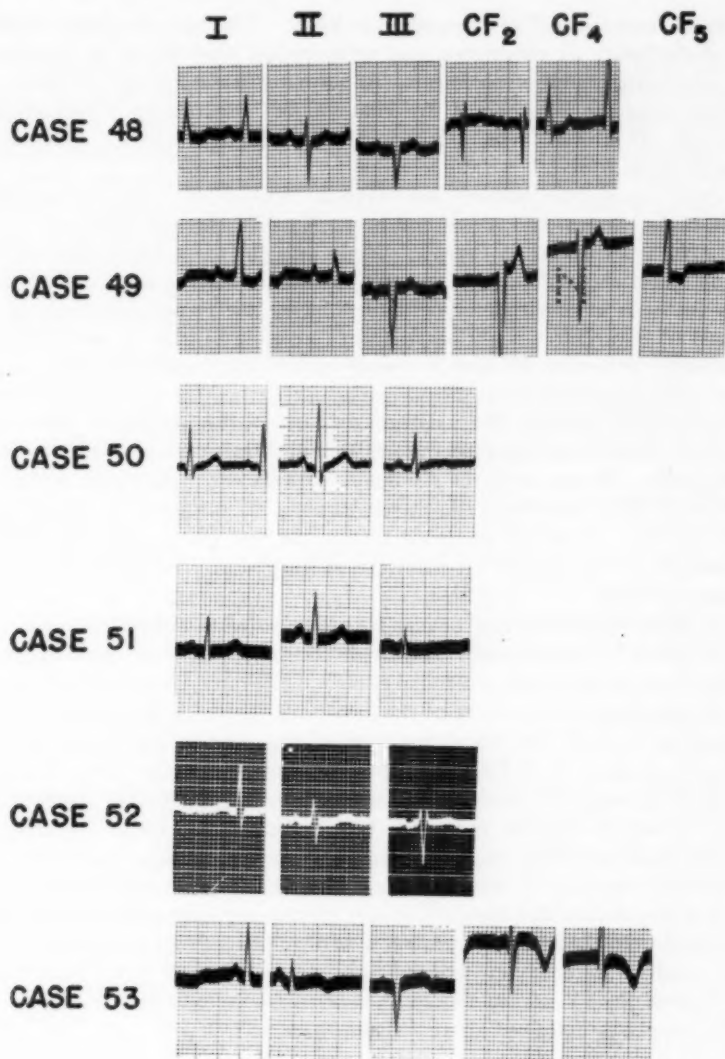


FIG. 8.

suggestive of the existence of congenital heart disease, though the precise nature of the lesion is indeterminate from the tracing alone.

Almost every type of electrocardiographic disturbance is found in association with congenital heart disease, and as a consequence, a very large

group of "non-specific" patterns could be listed. The most frequently noted are, disturbances of conduction and arrhythmias, particularly in auricular and ventricular septal involvement. Abnormal P wave findings in cases of marked auricular involvement are common but are readily distinguished from the "P mitrale" type. Occasionally low voltage is seen. However, these findings form a large vague group.

Two "non-specific" patterns are of special significance. The first is right heart strain pattern, and the second is the Katz-Wachtel phenomenon.

I. Right Heart Strain Pattern. Right axis shift is a normal finding in infancy until about the age of six months and is further noted, when the body diathesis is of slender type, either during the growth phase or as a normal adult variant. Right heart strain (see table 1) is never normal, and in infancy, or during the first few years of life, is almost invariably associated with congenital heart disease particularly when the QRS is 0.08 sec. or less. Unfortunately, the vast majority of cardiac anomalies, with the previously noted exceptions, produce right heart strain pattern in the electrocardiogram. Hence, from the standpoint of differential diagnosis, this pattern is of little importance; it merely denotes the presence of congenital heart disease. It should be added that in the age group when rheumatic endocarditis or its sequelae are manifest, another cause for right heart strain pattern is added.

II. Katz-Wachtel Phenomenon (Diphasic QRS Complexes). Katz and Wachtel²² observed, in a number of clinically diagnosed cases of congenital heart disease, that a peculiar electrocardiographic pattern was found. It was noted that two or three of the limb leads showed large diphasic QRS complexes in which the two phases were of the order of more than one to four, i.e., 1:3, 1:2 or 1:1. This finding, though pathognomonic for the existence of congenital anomalies, is nevertheless, a "non-specific" pattern in that it is not attributable to any one type of lesion. Schnitker¹⁵ noted its presence in 32 of 106 cases, about half of which were present in auricular or ventricular septal defect lesions, both complicated and uncomplicated.

It is emphasized that this finding is of greatest significance in infancy and childhood. In the older age groups, a similar picture may be produced by heart strain or coronary involvement.

Nine of the 53 cases in this series showed the diphasic characteristics of QRS complexes described above. These were as follows:

Cor triloculare biventriculare	1
Functional biloculate heart	2
Transposition of the great vessels	3
Coarctation of the aorta	1
Auricular septal defect	1
Von Gierke's disease	1
Total	9

CONCLUSIONS

Fifty-three cases of congenital heart disease were selected only on the basis that both electrocardiographic and postmortem records were available. As a result of this study and a review of previously reported cases, the proposal is made that the existence of congenital heart lesions may be suspected almost pathognomonically by a group of "specific" and "non-specific" congenital electrocardiographic patterns. The former is so termed because the electrocardiogram points to a particular congenital lesion. The latter, as the designation implies, suggests the existence of congenital heart disease but may be seen in a great variety of lesions. The "specific" patterns are produced by the following:

1. Dextrocardia—identified by the inversion of the major components of Lead I.

2. Anomalous origin of the left coronary artery from the pulmonary artery—identified by the pattern of anterior wall myocardial infarction in infancy.

3. Von Gierke's disease—identified by the presence of a combined heart strain pattern.

4. Lesions producing a left heart strain pattern:

a. those affecting the systemic outflow tract and aorta as aortic stenosis, coarctation of the aorta, etc., but not aortic atresia with underdeveloped left ventricle and mitral aplasia.

b. lesions of the tricuspid valve

1. tricuspid atresia;

2. Ebstein's disease

c. truncus arteriosus communis

d. single ventricle

The "non-specific" pattern of right heart strain (in contradistinction to right axis shift) is by far the most common pattern found. The Katz-Wachtel phenomenon, large diphasic QRS complexes in the limb leads, is a fairly frequent finding. Both of the preceding are noted in a great variety of congenital anomalies.

A number of cases are presented in tabular form to illustrate these conclusions.

I am indebted to Dr. O. Saphir for permission to use the necropsy protocols of the Department of Pathology and to Dr. L. N. Katz for his criticisms of this report.

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CASE REPORTS

SUPPURATIVE PYLEPHLEBITIS WITH BACTEREMIA IN CHRONIC ULCERATIVE COLITIS*

By JOSEPH FELSEN, M.D., and WILLIAM WOLARSKY, M.D., *New York, N. Y.*

SUPPURATIVE pylephlebitis with bacteremia complicating chronic ulcerative colitis is rare.¹ A review of 783 cases of chronic ulcerative colitis and ileitis under our care failed to reveal this complication in a single instance. Bargaen² reports one case of pylephlebitis among 1333 cases of chronic ulcerative colitis studied over a 10 year period. It occurred after ileostomy. Bockus³ mentions one case without bacteremia occurring two years after ileostomy for chronic ulcerative colitis and quotes a similar report by Elsom and Feder following ileostomy.

Intestinal infections are the most frequent precursors of suppurative pylephlebitis (Lichtman⁴). However, when suppurative appendicitis is removed from this group, the remaining intestinal lesions are only rarely implicated. The pathological process involves spread of the infection from the intestine along the branches of the mesenteric veins to the portal vein. There occurs an endo-, meso- and periphlebitis. In ulcerative colitis, the process is probably initiated in the submucosal branches of the mesenteric vein located within the infected bowel wall.

Clinically, suppurative pylephlebitis is characterized by pain in the epigastrium or right upper quadrant of the abdomen, accompanied by severe rigors and exhausting sweats. The temperature curve is of the "spiking" type seen in virulent bacteremias. Hepatomegaly is often present.

Positive blood cultures in chronic ulcerative colitis are rarely obtained during life, the few exceptions usually occurring just before death. This observation applies even during the stage of deep intramural infection when the pyrexia is of the septic type. Crohn and Schwartzman⁵ report positive blood cultures in three cases of chronic ulcerative colitis without pylephlebitis. The organisms obtained from the blood were anhemolytic streptococcus, hemolytic streptococcus and enterococcus respectively. Positive blood cultures during the course of suppurative pylephlebitis not associated with chronic ulcerative colitis are also unusual. Libman⁶ reported only one such instance in 15 cases studied. They occur when the thrombophlebitis involves the hepatic veins. The organisms reach the right heart, are transmitted by the pulmonic circulation and finally reach the left heart and the systemic circulation. *E. coli* and the streptococcus are the organisms usually implicated in order of diminishing frequency.

Following is a case report of suppurative pylephlebitis with bacteremia complicating chronic ulcerative colitis in a woman 62 years of age:

* Received for publication March 4, 1948.

From the Department of Laboratories and Research, The Bronx Hospital. The authors are indebted to Dr. Harry Wessler, Director of the Medical Service and to Dr. Max Weiss, Attending Physician, for the use of the clinical material in this case.

CASE REPORT

Present History: The patient was admitted to the Bronx Hospital on April 6, 1947 with chief complaints of pain in the left lower quadrant and diarrhea of three months' duration. The pain was constant and appeared to be relieved by defecation. The stools numbered three to five daily. They were watery and often contained blood and mucus. Vomiting occurred either during meals or immediately after.

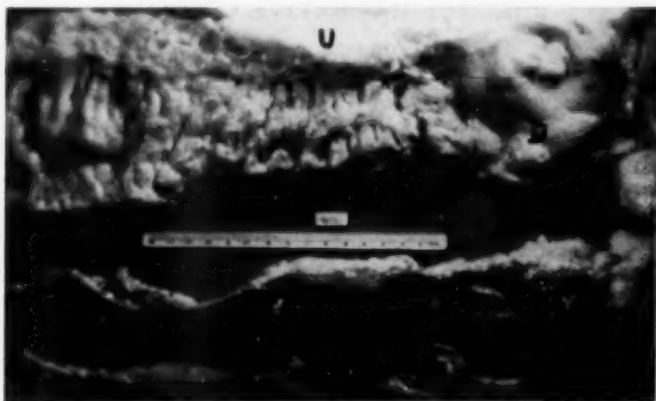


FIG. 1. Diffuse serpiginous and geographic ulceration of colon with pseudopolyps (U). The opening of a diverticulum is seen at D.



FIG. 2. Rectovaginal fistula. Metal probe is in the fistulous tract.

During the 48 hours prior to admission the vomiting and diarrhea were aggravated. The temperature rose to 104° F. on the day before admission. A weight loss of 20 pounds had occurred during the three months of illness.

Past History: Two and one-half years before the present illness, the patient experienced lower abdominal pain accompanied by bloody stools. Four to five

months before admission there were attacks of vertigo; and hypertension was noted.

Physical Examination: On admission the patient appeared acutely ill and toxic. There were moist crepitant râles posteriorly at the bases of both lungs. A systolic murmur was noted over the precordium, being most intense in the left para-sternal region. The blood pressure was 160 mm. Hg systolic, 80 diastolic, pulse 114, temperature 103° F. and respirations 22 per minute. The abdomen was distended and

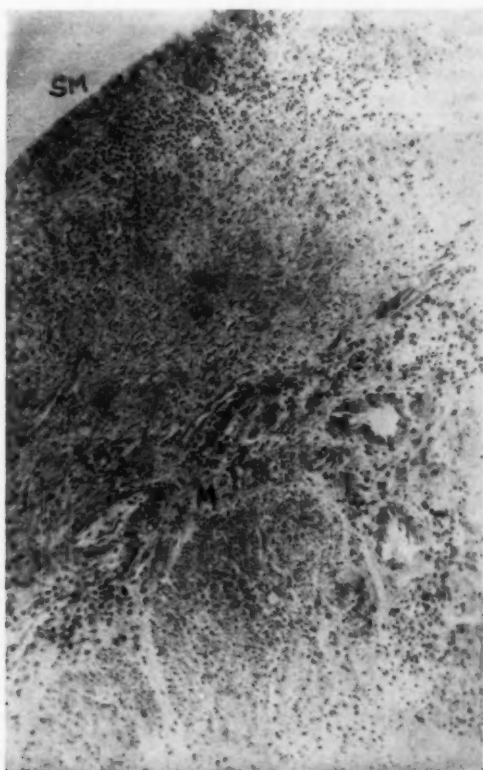


FIG. 3. Photomicrograph of section through wall of colon. The mucosal epithelium and solitary acuminate lymph nodules have disappeared. The floor of the ulcer is formed by submucosa (SM) which is infiltrated by polymorphonuclear, round and plasma cells. The cellular infiltration extends partly into the inner circular muscularis (M).

a sense of resistance was evident in the left lower quadrant. The liver and spleen were not palpable.

Laboratory Data: Urinalyses 2, 6, 7* revealed albumin trace, 1 to 2 red blood cells and 3 to 5 white blood cells per high power field with scattered epithelial cells.

Blood Counts: on the second,* fourth and fifth days, the hemoglobin averaged 79 per cent, erythrocytes 3,800,000, leukocytes 12,500 with mature neutrophils 70

* Figures indicate day of hospitalization.

per cent and band forms 30 per cent. Sedimentation rate (2) was 42 mm. (Win-trobe). Wassermann reaction, Kahn test (2*) negative.

Blood Chemistry:†

	Glucose	Urea N	N P N	Co. Comb. P.
2: *	112	17.1	28.0	51 vol. %
7			125.0	37.0 vol. %

Blood Culture (3*): *E. coli*—2 colonies per c.c. of blood. (4): *E. coli*—8 colonies per c.c. of blood.

Stool Examination 3*: Benzidine and guaiac tests positive for blood; no ova or parasites present.

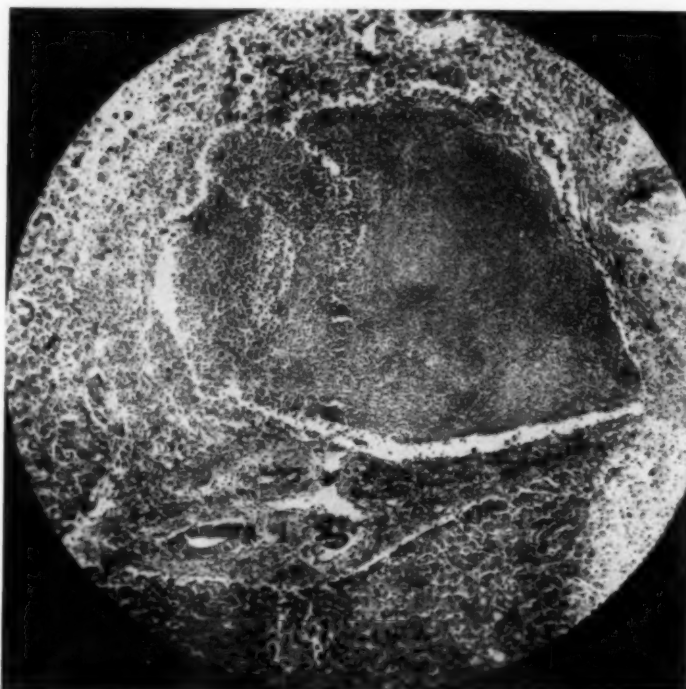


FIG. 4. Suppurative pylephlebitis involving portal radicle. Intact liver parenchyma is at bottom of picture.

X-Ray Examination (Dr. William Snow) (2*): Chest—no abnormality of the lungs. The heart shows moderate left ventricular enlargement. (4): Abdomen—no abnormality. No enlargement of the organs is noted. The intestines contain large amounts of feces.

Clinical Course: On the second day following admission, there was a rigor with a rise in temperature to 105.4° F. At that time the abdomen was distended and

† In mg. per 100 c.c.

tympanic. A marked sense of resistance was noted over the lower abdomen. Antipyretics were administered and the temperature fell to 101.8° F. four hours later. The rigor recurred the following day with a rise in temperature to 105.6° F. Thereafter, the pyrexia varied between 102° F. and 103.4° F. until death. Vomiting was marked and the patient developed urinary and fecal incontinence. Proctologic examination revealed a deep rounded ulcer at the anus measuring 2 cm. in size on the left anterolateral aspect. Extending from the edge of this ulcer the entire left lateral aspect of the anus was ulcerated. The critical condition of the patient precluded adequate sigmoidoscopy. Surgical intervention was deemed inadvisable. The patient received penicillin 30,000 units every three hours. This was changed to streptomycin 500 mg. every three hours when the blood culture revealed the presence of *E. coli*. Intravenous alimentation was instituted, using 5 per cent glucose in normal saline, 10 per cent glucose in distilled water and parenamine. The patient did not respond to therapy and died on the eighth day of hospitalization.

Necropsy Findings: (a) Gross pathology: The body was that of a white female, 165 cm. in length and 70 kg. in weight. When the peritoneal cavity was opened, there was present in the pelvis a moderate amount of brownish fluid with a fecal odor. The stomach was distended and contained a grayish-brown fluid. The large intestines were distended with gas. The serosa of the distal colon was covered with a purulent exudate. The left tube and ovary were adherent to the pelvic colon. The descending colon was looped down into the pelvis and presented two pin-point perforations. The mucosa of the colon, from the ileo-cecal valve to the anus, was diffusely ulcerated, exhibiting linear, serpiginous or geographic ulcers with pseudopolyposis. Just proximal to the ano-rectal junction, in the anterior midline, there was a well defined area of ulceration, approximately 1.5 cm. in diameter which communicated by a fistulous tract with the vagina. Numerous diverticula were present at approximately 45 cm. above the anus. In this general area two pin-point perforations extended through an ulcer. The meso-sigmoid was thickened and exhibited abscess formation. The mesenteric lymph nodes were enlarged and necrotic. Smears from the ulcers failed to reveal *E. histolytica*. The spleen presented the soft, mushy appearance of toxic splenitis. The liver was enlarged and pale. In the right lobe, anteriorly, there was a circumscribed abscess 1 cm. in size. The gall bladder contained six calculi of the mixed pigment type. Marked ulcerative atherosclerosis of the aorta was present. The myocardium of the left ventricle exhibited an area of fibrosis near the apex. The coronary arteries were the seat of a moderate degree of sclerosis. There were many cortical cysts present in the kidneys which were large and pale. There was an increase in the perinephric fat which was slightly adherent.

(b) Histopathology: **Liver:** Sections of the liver showed extensive suppurative pyelphlebitis involving even the smallest radicles of the portal vein, some of which were thrombosed. The vessel walls and adjacent hepatic parenchyma exhibited necrosis and cellular infiltration. The remaining intact parenchyma was the seat of fatty changes and cloudy swelling.

Kidneys: The convoluted tubules exhibited cloudy swelling. The interstitial tissue presented edema, round cell infiltration, fibroblastic proliferation and engorged blood vessels. Many of the glomeruli were hyalinized and some of the tubules were atrophic or destroyed.

Intestines: There was complete necrosis of the mucosa with marked mural fibrosis and infiltration by polymorphonuclear cells, lymphocytes, plasma cells, histiocytes and occasional multinucleated giant cells. This cellular infiltrate involved the entire bowel wall to and including the serosa. No *E. histolytica* were seen. Another section revealed, in addition to mucosal ulceration, marked pseudopolyposis of the remaining intact mucosa.

The case presented was complicated by the presence of two perforations in the descending colon, with associated peritonitis. Frank perforation of the intestine is uncommon in chronic ulcerative colitis. In our series of 718 cases of chronic ulcerative colitis, the incidence was 1.0 per cent. This complication generally proves fatal, due to peritonitis. Operative interference is usually of no avail since manipulation leads to a spreading infection of the peritoneum.

SUMMARY

A case of chronic ulcerative colitis is presented with unusual complications of suppurative pylephlebitis, *E. coli* bacteremia, perforation and peritonitis.

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PLEURAL EFFUSION PRODUCED BY ABDOMINO-PLEURAL COMMUNICATION IN A PATIENT WITH LAENNEC'S CIRRHOSIS OF THE LIVER AND ASCITES *

By M. HENRY WILLIAMS, JR., M.D., *New Haven, Connecticut*

PLEURAL effusion has been reported as an infrequent complication of cirrhosis of the liver.¹⁻⁸ It has been variously ascribed to coincidental tuberculosis or cardiac failure, to increase in capillary permeability, to hydrothorax as part of the generalized edema, to perihepatitis with spread to pleura and to ascitic fluid pressure causing insufficient pleural and pulmonary venous drainage.

In Ratnoff and Patek's series¹ of 386 cases of Laennec's cirrhosis, there were 25 patients with pleural effusion, 24 of whom had ascites. Of 102 patients with cirrhosis of the liver treated in the Presbyterian Hospital, 15 developed pleural effusion. Of these, eight had coincidental cardiac or pulmonary disease. Of the remaining seven cases, six had antecedent ascites. Conversely, 54 patients showed ascites for long periods of time (up to four years) without developing pleural effusion.

Frothingham⁷ recently reported a patient with cirrhosis of the liver with ascites, who suddenly developed a right pleural effusion of unusual severity.

* Received for publication July 3, 1948.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital in the City of New York.

Thoracentesis was performed 211 times with the removal of 467,100 c.c. of fluid, grossly identical to his abdominal fluid. Goodman⁸ reported a patient in whom massive pleural effusion developed after a severe automobile accident. This patient pursued a rapidly downward course with terminal development of jaundice and ascites. At autopsy cirrhosis of the liver was found together with a perforation in the right diaphragm which was considered to have resulted in the transfer of the patient's ascitic fluid to his right chest.

Limited experimental work has been done on the mechanism of the accumulation of pleural fluid in patients with ascites. Meigs⁹ demonstrated the passage of India ink from abdominal to pleural fluid in two patients with proved ovarian

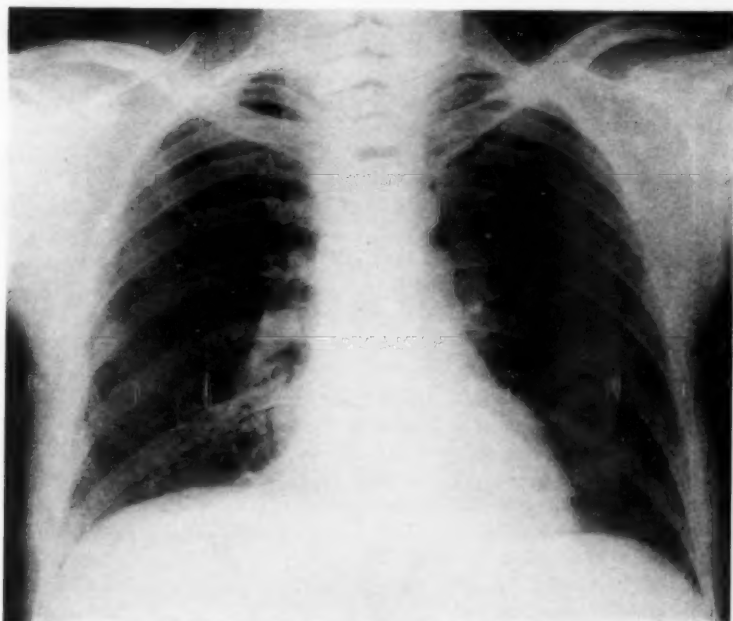


FIG. 1. Normal chest x-ray taken on the third day of a respiratory infection.

fibroma associated with ascites and pleural effusion. In one case, he failed to demonstrate passage of air from the abdominal to the pleural cavity. However, he did not perform a thoracentesis on this patient prior to induction of pneumoperitoneum. Meigs felt that fluid passed from the abdomen to the chest by way of diaphragmatic and mediastinal lymphatics. Rubin et al.¹⁰ supported this hypothesis by demonstrating that intra-abdominal injection of kaolin prevented the passage of dye from ascites to pleural effusion in a patient with Meigs' syndrome.

The following case is reported as an example of pleural effusion apparently due to rupture of the diaphragm in a patient with long-standing ascites due to Laennec's cirrhosis of the liver.

CASE REPORT

A 37 year old Irish widow entered the Presbyterian Hospital because of rapidly progressive abdominal swelling during the preceding five weeks. Her past history included a background of considerable alcohol ingestion. On physical examination the abdomen was found to be distended with ascitic fluid. The liver was enlarged to four fingers'-breadth below the costal margin on inspiration. The spleen was not palpated. Spider angiomas were present on the neck and shoulders. No edema of the extremities was evident.

Laboratory data included: Serum albumin 3 grams per 100 c.c.; negative cephalin flocculation test; two-plus thymol turbidity; alkaline phosphatase 5.5 Bodansky units; serum cholesterol 145 mg. per 100 c.c., with normal ratio of free to esterified fraction;

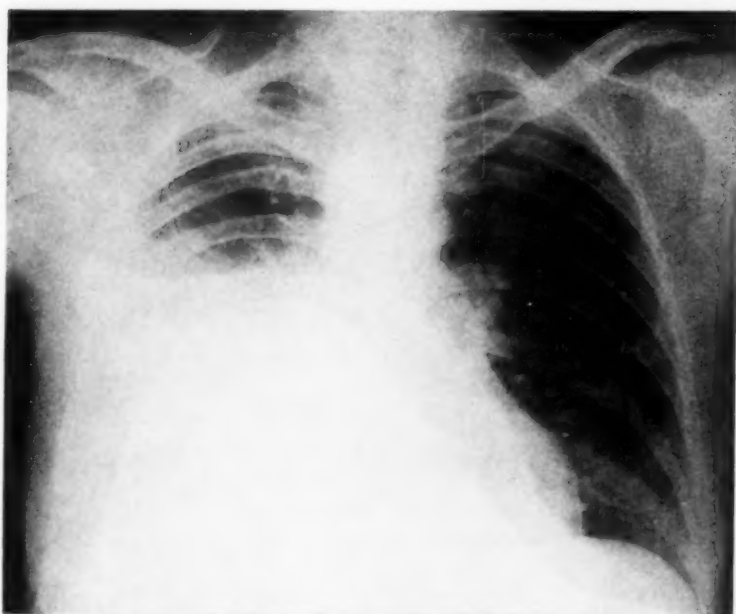


FIG. 2. Chest x-ray taken the following morning showing a right pleural effusion.

30 per cent retention of bromsulfalein 30 minutes after the intravenous injection of 5 mg. of dye per kg.; and serum bilirubin 0.8 mg. per 100 c.c.

Several paracenteses were performed with the removal of a progressively sanguineous transudate (table 1). Cultures of this material were repeatedly negative for tubercle bacilli and cell blocks failed to show tumor cells on three occasions. Because of the possibility of an ovarian tumor the patient underwent an exploratory laparotomy. No tumor was found. The liver was observed to be grossly typical of Laennec's cirrhosis and microscopic examination of a biopsy specimen confirmed this diagnosis. Postoperatively she remained asymptomatic for 81 days except for recurrent ascites. During the twenty-first week of her hospital stay she developed a dry, hacking cough with temperature elevation to 102°. Chest x-ray on the third day of

TABLE I
Characteristics of Abdominal and Thoracic Fluid

Date	Fluid	Specific Gravity	RBC/cu.mm.	Protein Gm. per cent
10/21/47	Ascites	1.018	less than one	
10/29/47	Ascites	1.015	450	3.3
2/15/48	Ascites	1.015	12,500	3.3
3/14/48	Pleural	1.017	7,520	4.4
3/29/48	Pleural	1.015	210,000	5.7

fever was normal (figure 1). On the following morning, however, physical signs of an extensive right pleural effusion were detected and confirmed by x-ray examination (figure 2). On the following day, 1000 c.c. of serosanguinous fluid, similar in character to the previously removed ascitic fluid (table 1), were removed from the right chest. Two days after the development of pleural effusion 5 c.c. of the blue dye T1824 were injected into the abdominal fluid. Thirty minutes after the injection

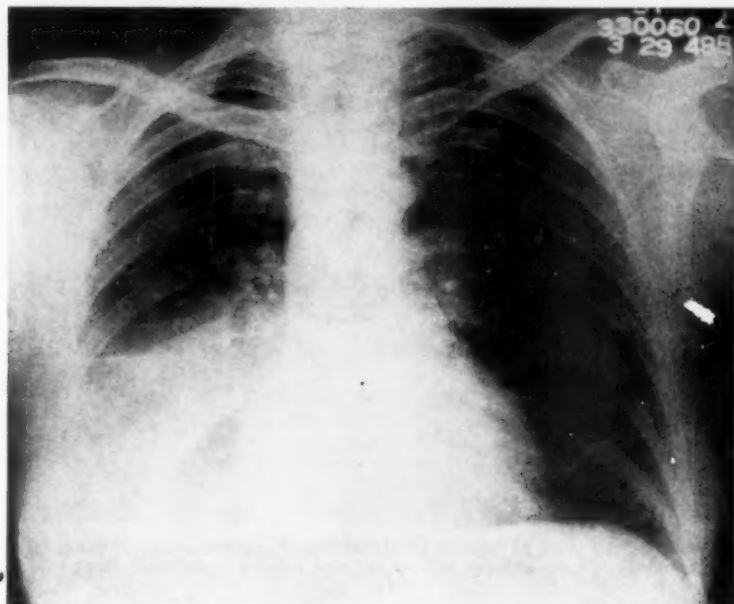


Fig. 3. Chest x-ray taken 16 days later, immediately after thoracentesis, to show that no air was present in the pleural cavity.

of the dye 1000 c.c. of thoracic fluid were withdrawn. There was no blue discoloration of this pleural fluid. One week later, following spontaneous disappearance of the cough and fever, 1000 c.c. of fluid were again withdrawn from the right chest and the same procedure of intra-abdominal instillation of T1824 was repeated. On this occasion chest fluid obtained 40 minutes after the injection of the dye contained large

amounts of blue material. Venous blood at this time contained no appreciable quantity of dye.

One week later 1000 c.c. of fluid were removed from the right chest following which a residual pleural effusion was still apparent by x-ray (figure 3). Fifteen hundred cubic centimeters of oxygen were then injected into the peritoneal cavity. Fifteen minutes after the pneumoperitoneum, chest x-ray was repeated (figure 4) and revealed a pneumothorax with 25 per cent collapse of the right lung.

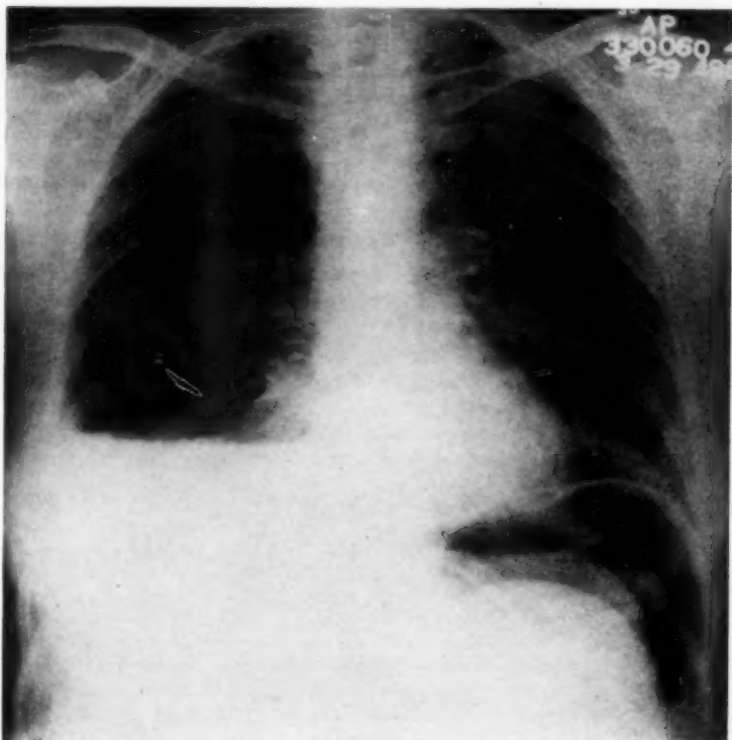


FIG. 4. Chest x-ray taken 15 minutes after induction of pneumoperitoneum demonstrating right hydropneumothorax with 25 per cent collapse of the right lung.

Comment: One case of pleural effusion due to rupture of the diaphragm in a patient with cirrhosis of the liver has been reported previously. In that instance the antecedent trauma to the chest was severe.

The present paper deals with an established case of Laennec's cirrhosis of the liver and ascites. The development in a few hours of a massive unilateral pleural effusion suggested the possibility of the development of a communication between the abdominal and pleural cavities. This was confirmed by the demonstration of the passage of dye and of air from the abdomen into the chest. The

antecedent long duration of ascites without pleural effusion and its unusually rapid appearance after a febrile episode with cough suggest the possibility of rupture of the diaphragm. It is conceivable that an underlying defect in the diaphragm led to this event, but evidence for inflammatory or neoplastic involvement could not be detected by x-ray and other studies.

SUMMARY

1. In a patient with Laennec's cirrhosis of the liver and ascites a peritoneo-pleural fistula became apparent following an episode of fever and cough.

2. Evidence for communication was obtained by the rapid passage of dye from the ascites into the pleural effusion and by the induction of a hydropneumothorax by the intra-abdominal instillation of oxygen.

3. The fact that pleural effusion is an uncommon complication of cirrhosis warrants a similar type of study in other patients with this condition.

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ACUTE INTRAVASCULAR HEMOLYSIS AND LOWER NEPHRON NEPHROSIS COMPLICATING ECLAMPSIA *

By R. W. KISTNER, M.D., and N. S. ASSALI, M.D., *Cincinnati, Ohio*

MASSIVE intravascular hemolysis with consequent hemoglobinemia, hemoglobinuria and renal failure is a rare complication of convulsive eclampsia. Dieckmann¹ mentioned hemoglobinuria briefly. Young² stated that cases of

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hemoglobinuria and eclampsia in which yellow pigment was observed in the collecting tubules have been reported in the German literature by Schmorl, Brütt and Schumm and others. These authors also gave a description of the renal failure associated with intravascular hemolysis. This hemolysis was attributed by them to the "poison" present in the patient's blood at the acme of the eclamptic attack.

Terplan and Javert³ and Licciardello and Stanbury⁴ noted acute hemolytic anemia following the use of quinine.

Young² and his associates reported in the English literature a series of cases of utero-placental damage in which there was acute renal failure leading to rapid death. Some of their cases showed hemoglobinuria and other pathological findings similar to those found in "crush syndrome" and incompatible blood transfusions. They concluded that the syndrome of renal failure following utero-placental damage is caused by a toxic material derived from tissue autolysis and that the shock present in many cases was a contributory factor.

Bratton⁵ observed cases of septic abortion subsequently followed by anuria.

Paxson et al.⁶ reported three cases of renal insufficiency following toxic separation of the placenta, uterine rupture and twisted ovarian cyst. They emphasized the similarity between these cases and the "crush syndrome" observed so frequently during World War II. They accepted Young's theory as being the etiological factor in the renal shutdown in these patients. Burwell, Kinney and Finch⁷ recently described a case of intravascular hemolysis and hemoglobinuria with renal complications following the use of an abortifacient paste.

An excellent coördination of all these syndromes in one pathological entity was made by Lucké.⁸ Under the common heading of "Lower Nephron Nephrosis," this author listed many etiological factors, among which were crush syndrome, burns, incompatible blood transfusion reactions, sulfonamide sensitivity, ingestion of toxic substances, prostatic resection, etc. Toxemia of pregnancy was also included as an etiological factor, but in the case discussed by Lucké, several blood transfusions had been given prior to the development of urinary shutdown.

However, an analysis of the reported cases in which pregnancy was complicated by acute renal failure revealed one constant finding, namely, utero-placental damage with infiltration of blood into the uterine musculature. Although all cases showed renal failure, very few demonstrated hemoglobinuria and hemoglobinemia. Furthermore, 90 per cent of the reported cases terminated fatally.

The following case is reported because of its rarity, differential diagnosis and favorable outcome.

CASE REPORT

A 20 year old colored female, gravida 1, para 0, was admitted to the receiving ward of the Cincinnati General Hospital at 10:30 a.m., June 30, 1948. She was comatose and the following history was obtained from the relatives.

Present Illness: At 9:00 a.m. on the morning of admission, the patient voided black urine. This was followed immediately by a generalized convulsion during which she fell to the floor and was noted to be "frothing at the mouth." Shortly after admission to the hospital, she had a second convulsion and fell off the stretcher, striking her right temple on the tile floor.

Past History: This was not contributory except that she had taken 60 c.c. of castor oil three days prior to admission. She had been followed in the pre-natal clinic, her first visit having been on January 21, 1948. Her last menstrual period was September 8, 1947, and the estimated date of delivery June 15, 1948. Her initial weight was 104 pounds and up to June 16 her weight gain was 18 pounds. The pre-natal course was uneventful, the blood pressure never having exceeded 110/70 mm. Hg. There was no albuminuria or other symptoms of toxemia.

The family history was relevant in that the patient's mother had died in the Cincinnati General Hospital in 1947 as the result of a ruptured aneurysm of the Circle of Willis which had occurred during the last month of pregnancy.

Physical Examination: Revealed a well developed, well nourished, comatose colored female. The blood pressure was 130/86 mm. Hg, the pulse rate 100, respirations 26, temperature 98.0° F. The skin was cool and moist. A large hematoma was seen over the right frontal area. Pupils were regular, equal and reacted well to light. Fundi could not be visualized. There was no nuchal rigidity. The chest was clear and the heart normal. The uterus was enlarged to full term size and contractions were palpable every six minutes. The uterine musculature relaxed well between contractions. The fetal heart could not be heard. Rectal examination revealed the cervix to be soft, effaced and 2 cm. dilated. The vertex was presenting in the left occiput anterior position and was well engaged. There were no edema or varicosities of the extremities. Neurological: right knee jerk +++++, left knee jerk +. Marked plantar reversal on the right. Otherwise normal.

Laboratory: Fifty c.c. of black urine were obtained by catheterization. Urinalysis: pH 5.5; specific gravity 1.020; albumin +++++. Emergency blood chemistry: urea nitrogen 9.6 mg. per cent, CO₂ 33 vol. per cent; blood uric acid 10.0 mg. per cent; clotting time 6 minutes, prothrombin concentration 62 per cent; serum protein 5.81 mg. per cent; red blood count 3.2 million, hemoglobin 11.5 grams, hematocrit 34 per cent. The serum after centrifugation was of a definite deep pink color. Roentgen-rays of the skull were negative. The patient was Rh positive and no sub-group agglutinins were demonstrable. The Donath-Landsteiner test for cold agglutinins and the "acid hemolysis test" (Ham) for paroxysmal nocturnal hemoglobinuria were negative. The fragility test was interpreted as suggestive of decreased red blood cell fragility.

Diagnosis: Because the patient was a primipara, at term, with no previous convulsive episodes and no history of drug ingestion, and because she presented: (1) evidence of intra-partum, intra-uterine fetal death, (2) mild acidosis, (3) hyperuricemia, (4) oliguria, (5) proteinuria, a diagnosis of term pregnancy in labor with eclampsia and concurrent acute intravascular hemolysis of unknown etiology was made. A provisional diagnosis of abruptio placenta was also made but was not believed likely because of the good uterine relaxation between contractions. The patient was given 10 minims of Veratrum viride hypodermically and 10 c.c. of 50 per cent magnesium sulfate intramuscularly and sent to the obstetrical pavilion. Intravenous 5 per cent glucose in water was started, penicillin, 50,000 units every three hours, and large amounts of vitamin K were given parenterally. A retention catheter was placed in the bladder to provide a better control of the urinary output.

Course: At 1:00 p.m. (three hours after admission) the patient, while still comatose, became extremely restless with her pains. One hundred mg. of Demerol were given and this was repeated at 4:00 p.m. when contractions were occurring every two minutes and the cervix was five centimeters dilated. Continuous intravenous fluids were administered throughout labor. Because of the extreme hemolysis and fall in blood pressure, and as a precautionary measure against possible post-partum hemorrhage, a transfusion of whole blood was started prior to delivery.

At 5:04 p.m. of the same day, she was delivered of a deadborn male infant by low forceps under pudendal block anesthesia. The placenta and membranes were expressed without difficulty, pitocin and ergotrate were given, and the uterus contracted well. The placenta showed no evidence of premature separation. There was no postpartum hemorrhage. Catheterized urine at the time of delivery was black and again revealed a four plus guaiac test, but no red cells were seen on microscopic examination. The blood pressure immediately postpartum was 124/76 mm. Hg and the pulse rate 96.

TABLE I
Hematologic Data

R.B.C.	3.2	—	2.34	1.75	3.27	—	3.77	—	4.18	3.93	3.93	3.77	2.35	3.63
W.B.C.	19,200	19,200	19,200	—	—	—	17,700	—	40,000	26,800	48,800	—	5,600	—
Hemoglobin	11.5	6.5	6.5	—	9.5	9.5	8.2	—	13	10.4	10.4	9.8	7.5	9
Hematocrit	34	21	21	13	—	—	—	—	34	—	—	—	36	—
Color of serum	pink	pink	pink	—	—	—	—	—	clear	—	yellow	—	—	—
after centrif.	—	—	—	—	—	—	—	—	yellow	—	—	—	—	—
Reticulocytes	—	—	3.5%	—	—	—	3.5%	—	—	1.3%	—	—	—	—
Platelets	—	—	86,580	—	—	—	331,760	—	—	503,040	—	—	—	—
Serum protein	5.81	—	3.38	—	—	—	4.42	—	4.59	—	—	—	5.3	—
Hospital day	1	2	3	4	5	6	7	8	9	10	11	12	13	14

At 6:30 p.m. the blood pressure was recorded at 80/70 and the pulse rate 102. The patient was still comatose, despite the fact that convulsions had not recurred. At 7:30 p.m.—two hours after delivery—she went into severe shock without apparent cause. There were no signs of internal or external hemorrhage. The uterus was still firmly contracted. Blood pressure and radial pulse were unobtainable. Carotid pulse was 112. A second unit of whole blood was started in a leg vein and a third unit was added to the transfusion which had been running since delivery. She was placed in shock position and oxygen was administered. Shock persisted for approximately two hours. By 9:30 p.m. the blood pressure had returned to 110/90, the pulse rate was 126 and feeble. Her general condition was slightly improved despite the persistent coma.

TABLE II
Urinary Data

Appearance	Black	Black	Black	Dark and cloudy	Red clear	Yellow	Yellow	Yellow	Yellow
Albumin	++++	++++	+++	++	++	+	0	Trace	0
Benzidine	++++	++++	+++	—	—	0	0	—	0
Guaiac	++++	++++	+++	—	—	0	0	—	0
pH	—	—	5	5	7	6.5	6	6	0
Specific gravity	1020	1020	1020	—	—	1009	1005	1005	1006
Red cells	0	6-8	8-10	1-2	1-2	2-5	1-2	0	0
White cells	0	6-8	1-2	loaded	0	occas.	1-2	1-2	0
Cast	0	1-2 granular	3-4 granular	granular	0	0	0	0	0
Hospital day	1	2	3	4	5	6	7	8	9

Because of the fall in the receiving ward, rapidly developing frontal and orbital hematomata and the subsequent finding of pupillary inequality and fixation, neurological and neurosurgical consultations were sought. The spinal fluid pressure was 320 mm. of water. The consultants believed the patient might have had a mild cerebral contusion which did not warrant surgical exploration. They attributed the coma to convulsive eclampsia complicated by acute vascular hemolysis and shock.

The progress of the case was as follows: For the first two days after admission, the patient continued to be comatose. Convulsions had not recurred. Hemoglobinemia and hemoglobinuria were still present. Her urinary output was low.

Tables 1 and 2 demonstrate subsequent hematologic and urinary data during the patient's stay in the hospital. Figure 1 illustrates her urinary output, fluid intake, blood chemistry and blood pressure variations.

From the third to the seventh postpartum day, the patient was almost completely anuric with frequent vomiting and other symptoms of uremia. She was delirious and in critical condition. Edema of the extremities and signs of ascites were detected.

After the eighth postpartum day diuresis began and there was a marked improvement in the patient's general condition. Edema and ascites disappeared, consciousness returned, the blood urea nitrogen dropped to normal. As figure 1 shows, there occurred a period of a marked compensatory polyuria coinciding with a fall in

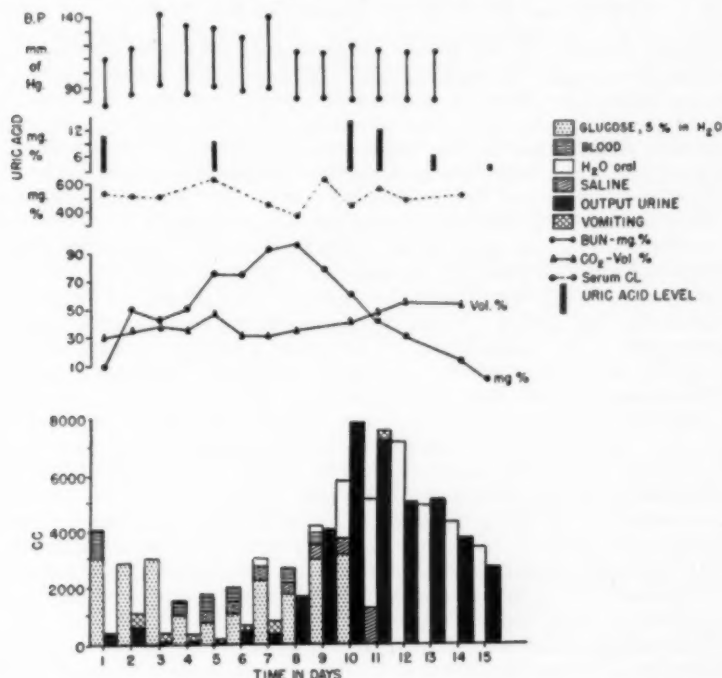


FIG. 1. The upper vertical columns represent the mean daily systolic and diastolic blood pressure variations. This was recorded every two hours for the first eight days and every eight hours thereafter. The blood pressure did not exceed 140/90 mm. of mercury. Blood uric acid level was constantly high and fell during the last few days. The serum chloride shows slight variation. The CO₂ combining power remained low up until the tenth day. The BUN rose sharply on the second day and followed closely the course of the anuria. The lower columns represent the intake in glucose and saline solutions, whole blood, plasma and water orally. The output of urine and vomiting are represented in the black and cross hatched columns.

the blood urea nitrogen and the plasma chlorides. This improvement continued steadily until the patient's discharge on her twentieth postpartum day. Liver and kidney function tests were performed on the eighteenth postpartum day and again six weeks after the patient's discharge. All were within normal limits.

DISCUSSION

The following features concerning the diagnosis and treatment of this case deserve consideration:

- a. What caused the acute hemolytic crisis?
- b. Did the patient have convulsive eclampsia?
- c. What caused the fetal death?
- d. Why did the patient go into shock?
- e. What was the etiology of the renal shutdown?
- f. What was the treatment of choice in this condition?

Evidence presented by the history and laboratory tests ruled out all of the usually known causes of hemolysis. Since the patient had ingested castor oil three days prior to her illness, a sample of this drug was obtained and examined by the Cincinnati Department of Health. It proved to be innocuous. Although the patient voided black urine before the convulsive seizure, and despite the lack of hypertension and visible edema, it seemed reasonable to assume that the hemolytic crisis was caused by a fulminating type of eclampsia. This diagnosis was corroborated by the excessive uricemia present on admission before azotemia had developed and by the intra-uterine death of the fetus. Most authors agree that fetal death in eclampsia is a consequence of placental damage or of the convulsions per se. There was no evidence of premature separation of the placenta to explain the fetal demise. Shock and renal suppression have been observed following acute massive hemolysis. There was no evidence to suggest that the shock in this patient was due either to internal or external hemorrhage or utero-placental damage. Lucké and others have shown that shock is an important determining cause in the development of lower nephron nephrosis. It is not the object of this paper to discuss the etiology of this disease. However, it seems evident that shock and acute massive hemolysis were the sole etiological factors in the causation of urinary suppression in this case.

In conclusion, we may assume that this patient had a fulminating form of eclampsia which produced acute, massive, intravascular hemolysis. A period of shock (with renal anoxia) followed which was of sufficient length to potentiate the development of tubular lesions, and the subsequent occurrence of the clinical entity known as lower nephron nephrosis.

The treatment of this case followed rather closely the procedure outlined by Burwell et al.,⁷ Thorn⁸ and Muirhead.¹⁰ It consisted of absolute control of the fluid and electrolyte balance as evidenced by daily determinations of the urinary output and necessary blood chemistries. The fluid intake consisted chiefly of intravenous 5 per cent glucose in distilled water, supplemented with small amounts of normal saline as needed. Additional saline was provided during the phase of compensatory polyuria when the plasma chlorides became lowered. Plasma and whole blood were given to correct hypoproteinemia and anemia. Particular attention was given to fluid and electrolyte balance during the phase of

compensatory polyuria, since deaths due to salt depletion have occasionally been noted.

The normal kidney function tests and urinalyses following the patient's discharge proved that the tubular lesion was reversible and the recovery was complete.

SUMMARY

1. A case of eclampsia complicated by an acute, massive, intravascular hemolysis and lower nephron nephrosis with complete recovery of the patient is presented.

2. The differential diagnosis and treatment are discussed.

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TWENTY YEAR FOLLOW-UP IN A CASE OF WOLFF-PARKINSON-WHITE SYNDROME *

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ELECTROCARDIOGRAMS exhibiting a short P-R interval and a prolonged QRS complex have been reported¹⁻⁴ long before the classical description of the syndrome by Wolff, Parkinson and White,⁵ and before the mechanism of the condition was recognized. The case to be reported here is one of the earliest instances, described by Hamburger in 1929 as showing bundle branch block.³

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CASE REPORT

M. S. was first seen when he was four and one-half years of age by the late Dr. W. W. Hamburger at this hospital in 1928 because of an acute respiratory infection and episodes of palpitation. A more detailed history may be found in the quoted paper and only one of his old electrocardiograms is reproduced here for comparison (figure 1). Apparently the patient recovered from this illness and was able to live a normal life. During World War II, when he was 19 years old, he served as a bomber pilot for three years, without any cardiac symptoms. In 1946 he was called to the Heart Station of the Michael Reese Hospital, Chicago, for a follow-up examination and several electrocardiograms then taken showed the persistence of the short P-R and prolonged QRS (figure 2), the contour being similar to the previous

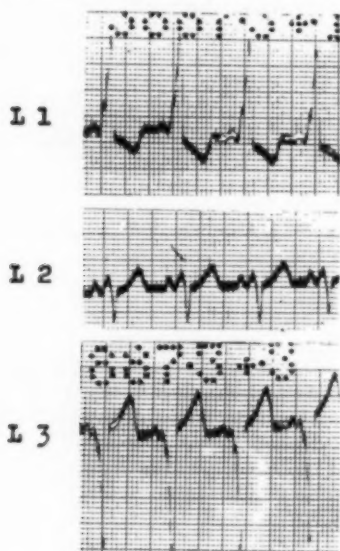


FIG. 1. Electrocardiogram taken in 1928 and interpreted as bundle branch block. (Shown by Hamburger,³ figure 57.)

electrocardiograms taken in 1928. In an effort to normalize his electrocardiogram, atropine sulfate (1/100 gr.) was given intravenously. Auriculo-ventricular dissociation ensued with the appearance of narrowing of QRS to 0.08 sec. and of deeply inverted T waves in Leads II and III (figure 3A). The reason for the inversion of the T waves is not apparent, but it is interesting that the sinus beats with normal QRS duration illustrated in 1929 also show a Q_s and a deeply inverted T_s . Several beats with a contour transitional between the wide and the narrow QRS complexes were recorded in Lead I (figure 4). This record was discussed in detail in a previous report dealing with the mechanism of fusion beats.⁶

Inhalation of amyl nitrite was followed by a sinus tachycardia with complexes showing a short P-R and a prolonged QRS (figure 3B). In Lead II, however, the QRS duration was only 0.10 sec. with a deep Q and an inverted T wave, indicating

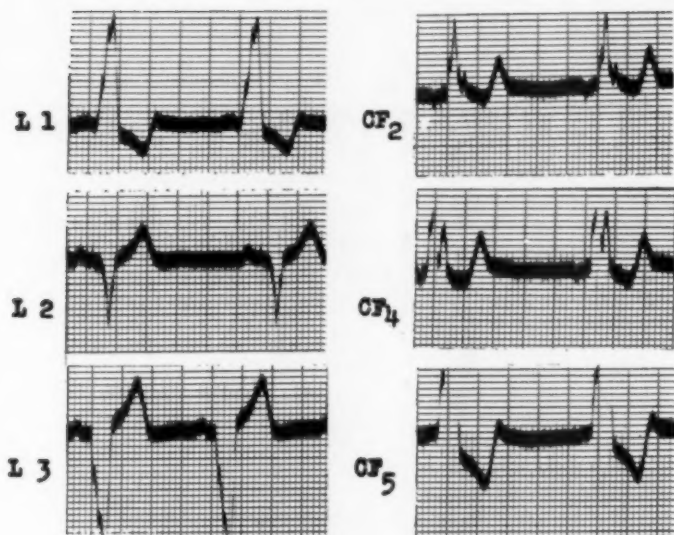


FIG. 2. Electrocardiogram taken May 25, 1946.

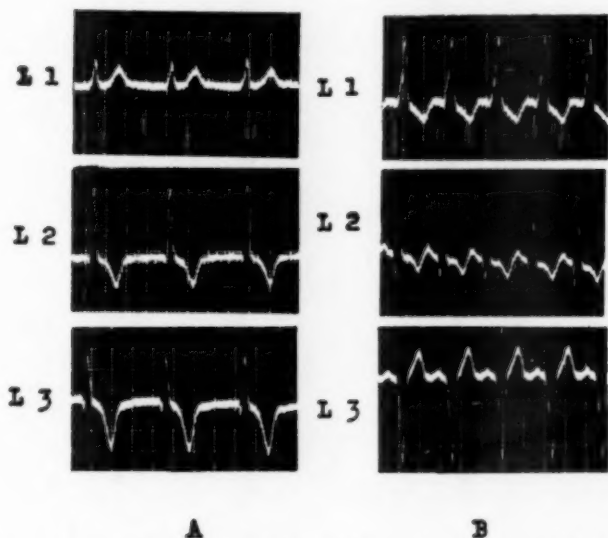


FIG. 3A. Electrocardiogram taken May 25, 1946 two minutes after 1/100 gr. of atropine sulfate intravenously. Discussed in text.

FIG. 3B. Electrocardiogram taken on May 25, 1946 immediately after inhalation of amyl nitrite. Discussed in text.

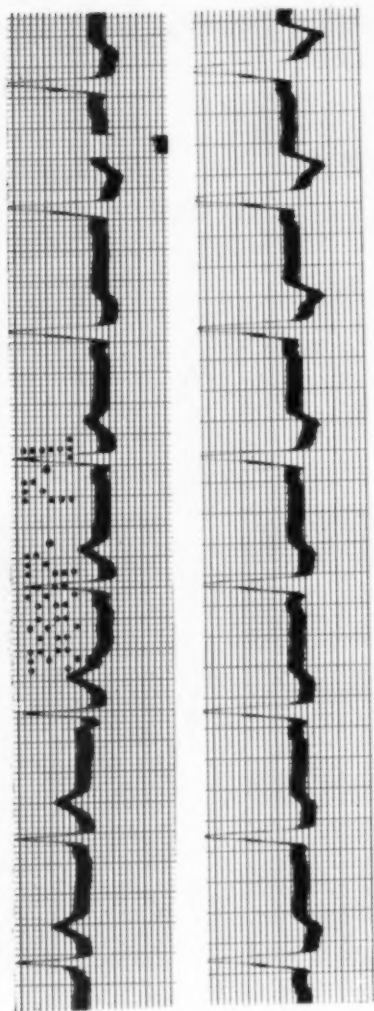


FIG. 4. Continuous strip of Lead I taken on May 25, 1946 immediately following the intravenous injection of 1/100 gr. atropine sulfate. The last beat of the upper strip is repeated at the beginning of the lower strip. This electrocardiogram has been reported by Malinow and Langendorf⁶ (figure 7). Discussed in text.

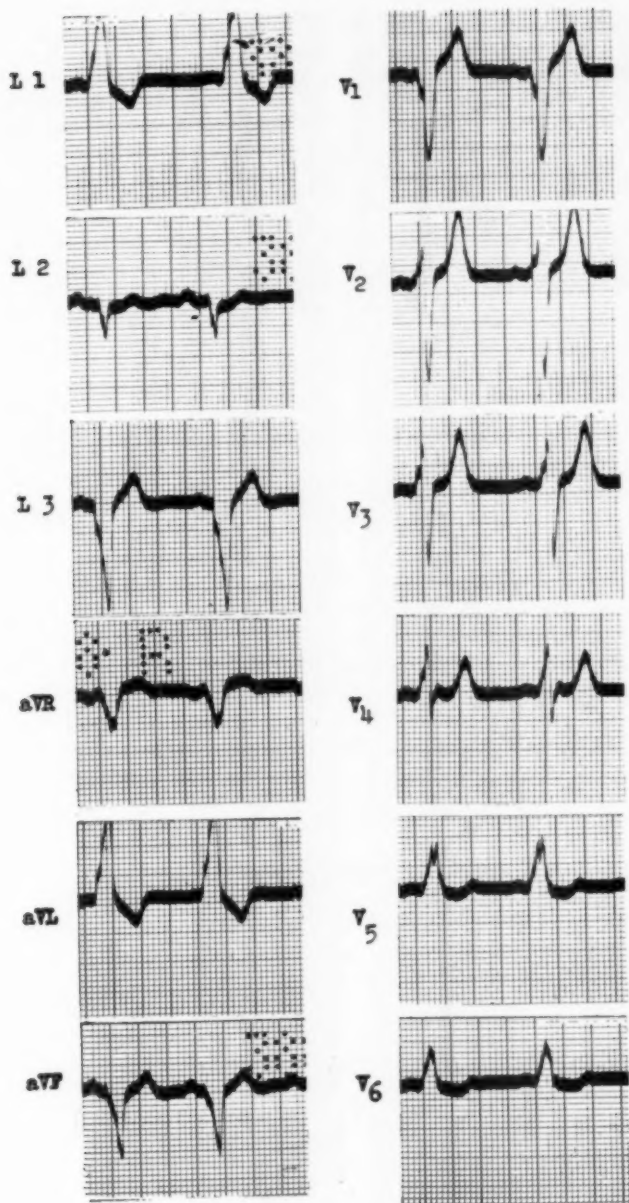


FIG. 5. Electrocardiogram taken on June 21, 1946.

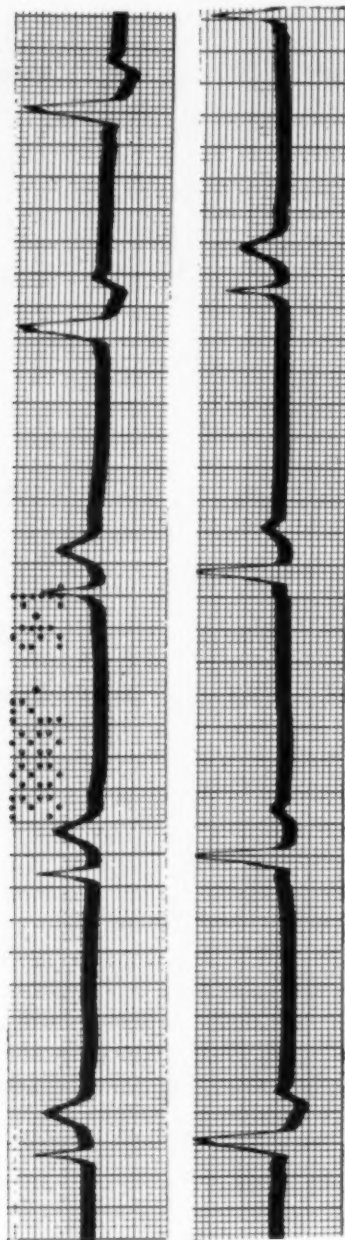


FIG. 6. Continuous strip of Lead I taken on June 21, 1948, immediately after 0.10 mg. of neosynephrin intravenously. The last beat of the upper record is repeated at the beginning of the lower one. Discussed in text.

a different spread of the impulse while Lead II was being recorded. The contour of the ventricular complexes in this lead is intermediate in form between that obtained after the administration of atropine and the control electrocardiogram taken the same day. This could be explained by assuming that amyl nitrite enhanced the conduction through the A-V node and the bundle of His giving rise to fusion beats without abnormal QRS prolongation.

Unilateral and bilateral pressure over the region of the carotid sinus did not greatly alter the contour of the electrocardiogram. With deep inspiration the QRS became smaller in Lead I, but this may have been due to positional changes.

In 1948, the patient was again called for a routine check-up. He was then 24 years old, did not have any cardiac complaints, and physical examination was entirely negative. An electrocardiogram showed the persistence of the W-P-W syndrome (figure 5). In a further attempt to obtain normal QRS complexes, 0.10 mg. of neosynephrin was injected intravenously.⁷ Sinus bradycardia with nodal escapes and a short period of A-V dissociation followed (figure 6). The nodal beats resembled those that occurred spontaneously in 1928 and after the administration of atropine in 1946 (figure 3A). A number of transitional complexes were recorded indicating different degrees of fusion of the two impulses spreading along both the normal and the accessory pathways.

An exercise test was performed, but no changes of the electrocardiographic contour occurred. Quinidine sulfate (0.8 gm.) was given by mouth, but the electrocardiogram did not revert to normal within the next two hours.

SUMMARY

A case of Wolff-Parkinson-White syndrome, reported in 1929 erroneously as exhibiting bundle branch block, is presented because it is apparently the case of Wolff-Parkinson-White syndrome with the longest electrocardiographic follow-up on record. The effect of several drugs on the electrocardiogram is discussed and illustrated. The long course in good health and the lack of other cardiac abnormalities speak for the benign nature of this condition in the absence of attacks of paroxysmal tachycardia.

We wish to express our appreciation to Dr. L. N. Katz for his valuable suggestions.

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PERIRENAL LYMPHANGIOMA CAUSING HYPERTENSION *

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THE literature on the subject of perirenal lymphangioma is extremely scanty. An excellent article with review of the subject has been presented by Kretschmer.² Peripelvic cysts, which are large lymphatic cysts of the kidney, have been described very thoroughly by Henthorne,¹⁰ and recently in an article by Scholl.⁹ The purpose of this presentation is to report another case of unilateral pyelonephritis resulting from compression of the left renal pedicle by a cavernous lymphangioma . . . with subsequent development of severe hypertension. Death resulted from an intracerebral hemorrhage.

CASE REPORT

A 47 year old colored male janitor was first admitted to Gallinger Municipal Hospital on July 9, 1947 with a history of becoming suddenly unconscious that morning while working. This was followed by a right-sided hemiplegia. His wife claimed that hypertension was first detected about six months previously by a private physician. At that time he complained of a "slight stroke" which disappeared after two weeks of bed rest. During the present hospital admission physical examination showed a mentally confused, lethargic colored male replying to questions with the words "OK." There was a vacant expression on the face. Blood pressure was 254/138 mm. Hg. The pupils were equal and measured two millimeters in diameter, and the retina showed Grade II hypertensive changes. There was a coarse tremor of the tongue which on protrusion deviated to the right. The heart was slightly enlarged to the left. The second aortic sound was louder than the second pulmonic. The right forearm was spastic. Clonus and a positive Babinski sign were present on the right side. While in the hospital he rapidly improved, and on the date of discharge, July 28, 1947, he was mentally clear and able to control his speech, bladder and bowel. Some of the muscular control in the right upper extremity returned.

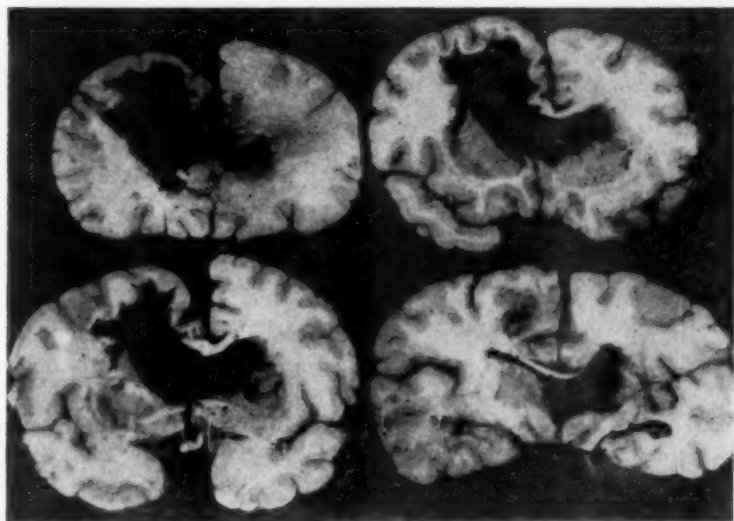
At home the patient remained in bed until November 18, 1947 during which time he was receiving physiotherapy to the right side. He improved very gradually. He visited the Neuropsychiatric Clinic at Freedmen's Hospital for follow-up studies. Physical examination on January 5, 1948 revealed a thin, undernourished, colored male with residual right hemiplegia. Blood pressure was 200/100 mm. Hg. The right pupil did not react to light, but both pupils reacted to accommodation. Neurological examination showed weakness and retraction of the mouth on the right side; gag reflex depression; and weakness of the right arm and leg. There was a positive Babinski reflex and clonus on the right side.

On January 11, 1948 the patient was re-admitted to the Gallinger Municipal Hospital in a comatose state. He retired to bed the night before in good condition, but was found the next morning in an unconscious state. Physical examination revealed a comatose colored male with frothy blood oozing from his mouth and nose. Breathing was stertorous. Blood pressure was 230/120 mm. Hg. The heart rate was irregular at 132 beats per minute. The pupils were equal but did not react to light or accommodation. No reflexes could be elicited. No laboratory work was done. The patient died in the admitting office.

Essential Autopsy Findings: When the cranial cavity was opened clotted blood was seen in the subarachnoid space. There was a defect in the brain substance of the left frontal area on the superior surface about the region of the prefrontal fissure.

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Fresh blood was oozing from this defect. The base of the brain was also covered with clotted blood. The foramina of Luschka contained clotted blood. Cut section of the brain revealed a massive intracerebral hemorrhage (figures 1 to 4). Beginning at the lateral basal ganglionic mass of the left side (figure 4), the hemorrhage had destroyed the left putamen, pallidum, body of the caudate nucleus, body of the corpus callosum, fornix, part of the centrum ovale, the internal capsule, thalamus, and the subthalamus. Due to an old infarct there was also involvement of the external capsule and claustrum in this region. The hemorrhage had broken through the septum pellucidum to the opposite side (figure 3), destroying the greater part of the head of the caudate nuclei of both sides and a great part of the centrum ovale on the right side. It extended above the internal capsule to the cortex of the medial and lateral surface of the frontal lobe. The hemorrhage had also broken through the anterior



FIGS. 1-4. Gross photographs of the intracerebral hemorrhage and old infarct described in the text.

commissure, the lamina terminalis and the floor of the third ventricle. Extensive destruction of the centrum ovale on the right side, the head of the caudate nucleus, and the genu of the corpus callosum (figures 1 and 2). Microscopically, there was hemorrhage and destruction of brain tissue with early phagocytosis. The arterioles showed marked intimal hyalinization and medial hypertrophy (figures 5 and 6). The gross distribution of hemorrhage around the lateral ventricles, the microscopic findings of dilated venules occasionally containing fibrinous thrombi, and numerous perivenous hemorrhages suggest a venous origin for the hemorrhage (Scheinker¹¹).

The heart weighed 420 grams. The left ventricle was much firmer and thicker than usual. It measured 23 millimeters in thickness. The valve rings were slightly dilated. The coronary arteries showed moderate arteriosclerosis. The coronary ostia were smaller than normal. The aortic valve showed slight calcification at the bases of the leaflets. Microscopically, the myofibrils were hypertrophied. The



FIG. 5. Photomicrograph of brain showing hemorrhage, and perivascular mononuclear cell infiltration ($\times 100$).

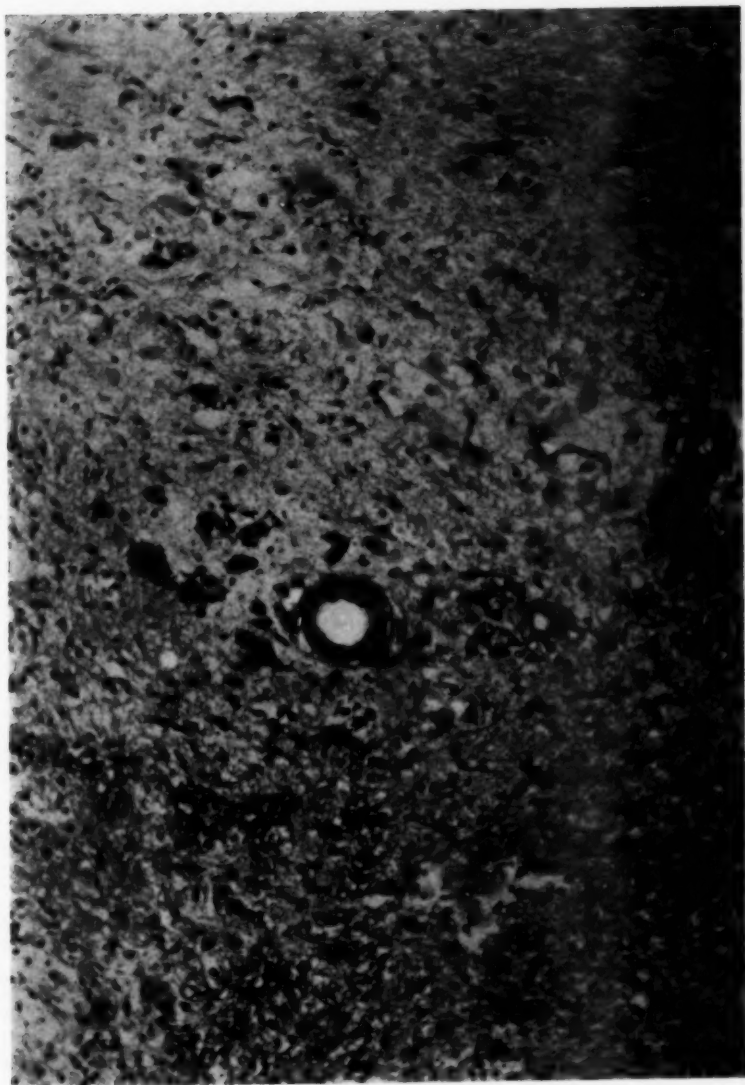


FIG. 6. Photomicrograph of brain showing marked thickening of arteriole ($\times 450$).

arterioles were thickened as described in the brain. The aorta was markedly sclerotic.

When the abdominal cavity was opened there was seen a tumor composed of many irregular, gray-white, papillary cystic masses growing from the lateral portions of the vertebral column in the retroperitoneal space at the level of the first to third lumbar vertebrae. The cysts of the tumor measured a maximum of about 1.5 centimeters, and contained a slightly cloudy serous fluid. A striking feature was the fact that the tumor completely encircled the left renal hilus and apparently compressed the vessels and pelvis of the kidney. The ureters were not dilated. One portion of the tumor was seen below the right kidney hilus and was continuous with the main tumor mass of the left side being connected behind the aorta and vena cava (figure 7). Microscopically, the tumor was composed of many thin-walled spaces lined by a layer of flattened endothelial cells (figures 7 and 8). These spaces proliferate near lymphoid follicles. This is the appearance of a typical cavernous lymphangioma (figures 8 and 9).

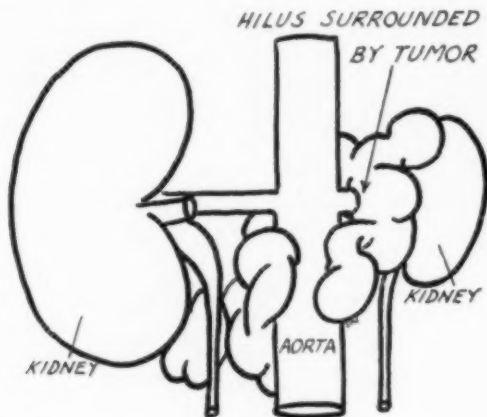


Fig. 7. Diagram of location and estimated appearance of the cavernous lymphangioma described in text.

The right kidney was enlarged weighing 210 grams. The only important feature after gross and microscopic examination was the marked thickening of the arterioles, occasional hyalinization of the glomeruli, and focal accumulations of lymphocytes.

The left kidney was very small weighing 40 grams. It was irregular in shape and much firmer than usual. Cut section revealed alternating, irregular, pale, firm areas, and softer red areas. The capsule was densely adherent to the cortex. Microscopically, many colloid-filled, dilated tubules are seen in some areas of the section (figure 10). The more normal areas show congestion of glomeruli. The abnormal areas resemble thyroid tissue.

The adrenals were slightly enlarged and grossly showed a firm, gray medulla slightly thicker than usual. Microscopically, the cells of the medulla were much larger than usual, stained deeply basophilic, and contained irregular hyperchromatic nuclei. The vessels were markedly thickened.

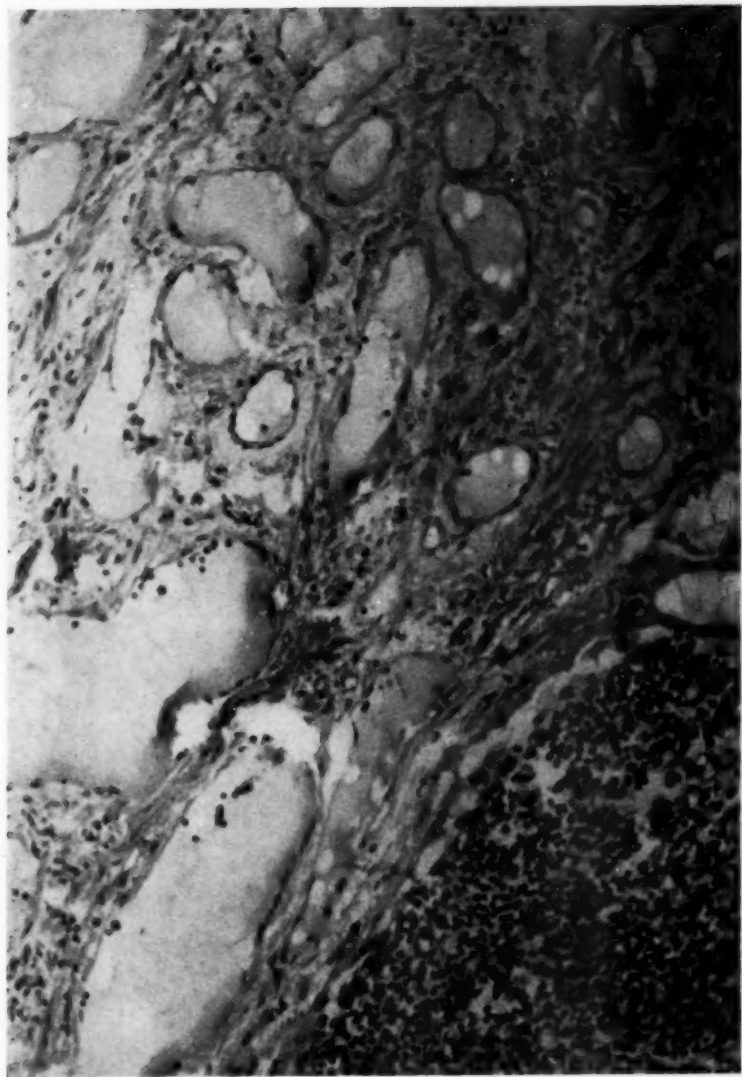


FIG. 8. Photomicrograph of cavernous lymphangioma. Note the lymphoid tissue and the presence of many spaces containing lymph and lined by a single layer of flat cells ($\times 100$ and 450).

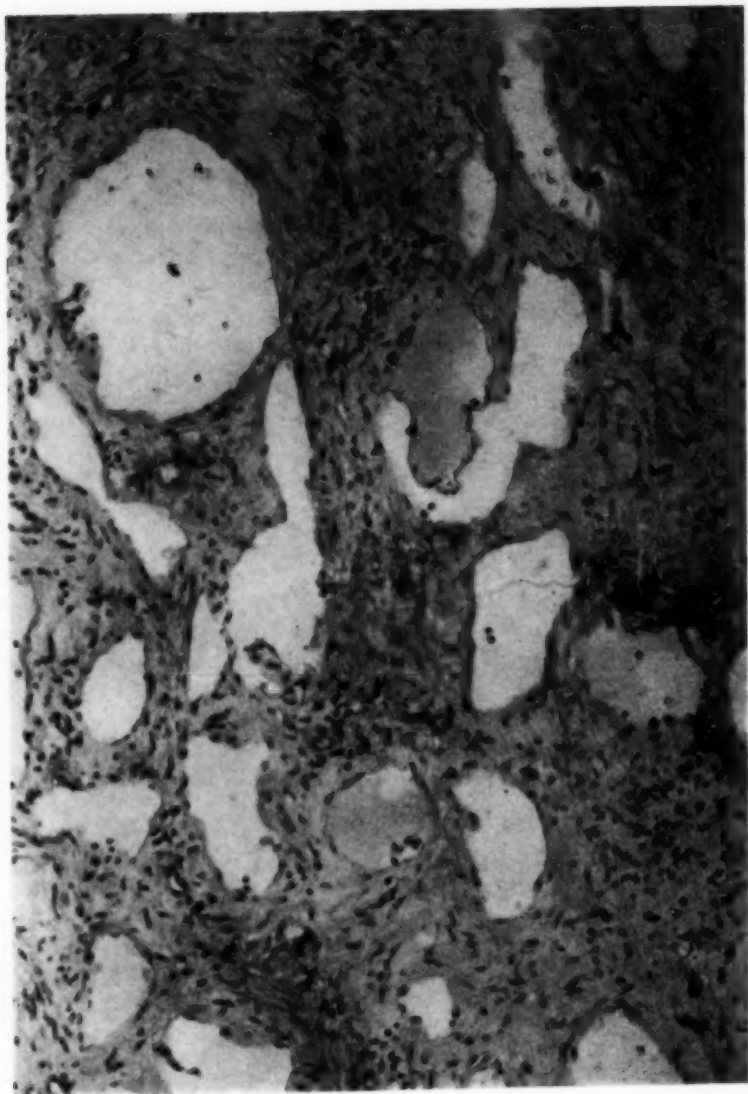


FIG. 9. Photomicrograph of cavernous lymphangioma. Note the lymphoid tissue and the presence of many spaces containing lymph and lined by a single layer of flat cells ($\times 100$ and 450).



FIG. 10. Photomicrograph of the markedly dilated tubules of the left kidney ($\times 100$).

COMMENT

Lymphangioma is a tumor composed of variable sized spaces containing lymph and lined by endothelial cells. It is a slow-growing tumor usually congenital in origin. They are more common in children. The tumor may be single or multiple, cystic or cavernous. If cavernous, it is further subdivided into hypertrophic and diffuse systemic types. Because of its slow growth the tumor is relatively benign until adult life. It grows near primitive centers of tissue, probably arising from small segments of lymphoid tissue retaining an embryonal character. There is some reason to believe that remnants of the renal lymph sacs are responsible for lymphangiomas in abdominal or retroperitoneal regions in the manner that the jugular lymph sacs are responsible for cystic hygromas in the neck. The tumor may appear in the skin and in the deep areolar and connective tissue of the lip, tongue, neck, mediastinum, mesentery, omentum, retroperitoneal and perirenal areas. Most of the abdominal lymphangiomas occur in the omentum and may become enormous in size. The tumor described in this case is a cavernous type of cystic lymphangioma probably arising from the renal lymphatics just below the cysterna chyli. The tumor appeared to be distributed about the blood vessels in the position of the larger hilar lymphatics.

Kreutzman¹ in discussing hypertension due to unilateral renal disease showed that chronic pyelonephritis is the most common cause followed by solitary renal cysts. He also states that in order to obtain relief of hypertension after surgical removal of the kidney, one must know: (1) That the condition is not one of essential hypertension. (2) No reduction in blood pressure will occur if the affected kidney is functionless. (3) The arterial pressure must be persistently elevated. (4) The hypertension must be less than two years in duration in order to obtain a cure. However, relief of symptoms or an arrest of the disease may ensue in long standing cases after surgery. (5) The opposite kidney must be normal.

In this case it is believed that the cystic lymphangioma was present since birth. Recurrent episodes of pyelonephritis of the left kidney resulted in the small, shrunken, fibrotic kidney which is typical of a chronic atrophic pyelonephritis. Reports have been published of hypertension subsiding to normal levels after surgical removal of the diseased kidney in unilateral atrophic pyelonephritis. It is believed that this case would have responded to such treatment. Once the hypertension became sustained at a high level, the complication of intracerebral hemorrhage followed and caused death.

SUMMARY

1. A case of hypertension caused by a perirenal cavernous lymphangioma compressing the left renal vessels and pelvis is reported. Atrophic pyelonephritis and nephrosclerosis (arteriolar) were present. Death resulted from intracerebral hemorrhage.

2. A brief review of the literature is presented.

3. In cases of hypertension it is hoped that this etiological factor is considered in the diagnosis, for cure may follow after surgical removal of the diseased kidney.

I acknowledge with sincere appreciation the help rendered by the following in preparing this article: Dr. Charles F. Geschickter, Prof. Pathology; Dr. Othmar Solnitzky, Prof. Anatomy; Dr. Vincent Dardin, Clin. Prof. Pathology; and Dr. Samuel P. Hicks, former Associate Prof. Pathology, all of Georgetown University School of Medicine, Washington, D. C.

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UNILATERAL RENAL GLYCOSURIA IN ASSOCIATION WITH DIABETES MELLITUS AND CHRONIC PYELONEPHRITIS *

By CLAUDE P. CALLAWAY, M.D., *San Francisco, California*

ALTHOUGH there appear to be no reports of *unilateral* renal glycosuria, with or without the association of the diabetic state, glycosuria of renal origin concomitant with diabetes mellitus has been observed. Vogelenzang¹ studied a patient in whom the postprandial hyperglycemia and clinical symptoms of diabetes were present who nevertheless showed a significant glycosuria when the blood glucose level was at or below normal levels. Voigt² described a diabetic individual with glycosuria at a blood glucose level of 80 milligrams per hundred cubic centimeters of blood. Curran and Mills,³ Holst,⁴ and Dogliotti⁵ reported similar cases. A patient discussed by Lozinski and Frohlich⁶ maintained glycosuria until the blood glucose level had fallen to 65 milligrams per hundred cubic centimeters of blood. Monasterio⁷ reviewed the subject in 1941. In none of these instances is there any mention of renal disease.

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The patient to be reported was one in whom the control of diabetes mellitus was difficult because of hypoglycemia with insulin reactions coincident with glycosuria. It was repeatedly demonstrated that the glycosuria was entirely unilateral. Because of this and of the evidences of coincident ipsilateral pyelonephritis, the affected kidney was removed. After nephrectomy, the glycosuria of renal origin was absent and the diabetes mellitus was easily controlled.

CASE REPORT

The patient, a married woman, had always been in good health until June, 1935, when at the age of 25 she suffered five days of chills, fever, pain in the right flank, and dysuria. In November, 1935, she began to lose weight, noticed polydipsia and polyuria, and developed a craving for sweets. By February, 1936, she had lost 48 pounds in weight, and was admitted to another hospital in coma. Glycosuria was noted as four plus; the blood glucose level was 536 mg. per cent. Convalescence was prolonged to three months because of difficulty in controlling her diabetic state. She experienced at least 20 insulin reactions, some of them coincident with heavy glycosuria.

During that hospital admission, gross pyuria was observed and staphylococci were recovered from the right ureter, though none was isolated from the left. Retrograde pyelograms outlined a huge right kidney pelvis with blunted calyces. The left kidney pelvis was questionably enlarged but the calyces appeared to be normal. There was ureteral obstruction on the right, none on the left. Her blood pressure at that time was 120 millimeters of mercury systolic and 70 millimeters diastolic.

After dismissal she did not regain strength or feel well and continued to maintain a heavy glycosuria. She was admitted to Stanford Hospital for a three day period in January, 1937. All examinations of urine were recorded as four plus, save on one occasion when a coincident blood glucose level of 47 mg. per cent was noted. Bladder urine culture showed staphylococci.

In September, 1937, she was admitted to another hospital where a phenolsulfonphthalein excretion test was recorded as 4 per cent of dye from the right ureter and 43 per cent of the dye from the left ureter recovered in 30 minutes. Two months later, 14 per cent of the dye was recovered from the right ureter and 15 per cent from the left ureter in 30 minutes. Retrograde pyelograms at that time failed to visualize the right kidney because of obstruction of the ureter. The left kidney pelvis appeared normal.

The patient continued to feel ill. Glycosuria persisted, and she felt nervous and restless when the urine did not contain glucose. Many schemes of insulin dosages were tried without success. Polyuria and nocturia persisted. Following several months of alternation between repeated insulin shocks and acetonuria, during which time she lost seven pounds in weight, she was admitted to Stanford University Hospital on April 28, 1947.

Physical Examination: The patient, a 38 year old woman, was thin and appeared tired. Weight was 103 pounds; height was 63 inches. The blood pressure was 210 mm. of mercury systolic and 110 mm. diastolic. Fundi were not abnormal. The heart and lungs were normal. The right kidney was palpable. There were no other positive findings.

Laboratory Observations: The hemoglobin concentration was 15 grams per hundred cubic centimeters of blood. The packed cell volume was 41 per cent. The red blood cell count was 5.3 million cells per cubic millimeter of blood. The white blood cell count was 10,560 cells per cubic millimeter of blood. A differential count showed 66 per cent segmented forms, 12 per cent banded forms, and 22 per cent

lymphocytes. The erythrocyte sedimentation rate (Wintrobe) was 26 millimeters per hour. The blood urea level was 39 mg. per cent. The whole blood cholesterol level was 295 mg. per cent. The fasting blood glucose level the morning following admission was 182 mg. per cent.

Routine examinations of bladder urine obtained by catheter showed no casts or erythrocytes, but 20 to 30 leukocytes per high dry field were noted in each uncentrifuged specimen. There was no albuminuria. Urine from a right ureteral catheter specimen contained glucose and leukocytes, that from the left contained neither. A specimen of bladder urine collected by catheter during a one hour period contained in excess of 1 per cent glucose. The blood glucose level at the beginning of the hour was 75 mg. per cent.

Ureteral catheters were introduced three hours after the patient had been given a dose of insulin calculated to maintain the blood glucose level between 150 and 200 mg. per cent. After the catheters had drained for 30 minutes in order to allow any urine retained in the renal pelves to escape, the collection of one hour samples was begun. From the right kidney 145 cubic centimeters of urine were obtained which

TABLE I

Time in Minutes	Vol. c.c.		Urinary Glucose %		Blood Glucose Mg. %
	Right	Left	Right	Left	
0-5	11	28	None	.88	82
5-10	12	38	None	.72	
10-15	10	18	None	.60	
15-20	9	6.5	None	.48	
20-25	7	9	None	.48	
25-30	6	8	None	.24	60
30-35	3	4	None	.24	
35-40	3	4	None	.10	
40-45	4	6	None	.10	
45-50	1.5	4.5	None	.00	
50-55	4	3.5	None	.00	50
55-60	2	5.5	None	.00	
	72.5	135.0			

held 3.4 per cent of glucose, a total of 4.95 grams. From the left 70 cubic centimeters were recovered which contained only 0.4 gram of glucose, 0.6 gram per hundred cubic centimeters of urine. Blood glucose level at the commencement of the observations was 150 mg. per cent and at the close 215 mg. per cent.

A dose of insulin expected to maintain the blood glucose level at about 120 mg. per cent was given. After the ureteral catheters had been in place for 30 minutes, urine was collected from each catheter every five minutes for a period of one hour. Blood glucose determinations at 0, 30, and 60 minutes after the start of collections were 82, 60, and 50 mg. per cent respectively. During this interval the left kidney excreted no glucose. On the right the initial concentration of glucose in urine was 88 mg. per cent. As time elapsed, the amount and concentration of glucose in urine fell as indicated in table I.

Urea clearance by the left kidney was 126 per cent of normal maximal clearance for one kidney. Urea clearance from the right kidney was 112 per cent of maximal clearance for one kidney. During the one hour period of this procedure the left kidney excreted 210 cubic centimeters of urine, the right 337 cubic centimeters of urine.

The left kidney cleared 105 cubic centimeters of blood per minute and the right 33 cubic centimeters of blood per minute during a one hour period.

The left kidney cleared 48 cubic centimeters of blood creatinine per minute; the right kidney cleared 53 cubic centimeters of blood per minute.

Phenol red excretion tests showed that the dye appeared on the left in seven minutes and on the right in 20 minutes after injection. The left kidney excreted 15 per cent of the dye in 30 minutes, the right 2 per cent.

Bacteriological studies isolated 500,000 colonies of coagulase negative *Staphylococcus albus* per cubic centimeter of urine from a right ureteral catheter at the first examination, and 10,000,000 colonies at a later culture. On the left, only 350 and 60 such colonies were obtained on the same occasions.

Retrograde pyelograms outlined marked dilatation of the right kidney pelvis with blunting and deformity of the calyces. The upper calyx of the left kidney seemed longer than usual, but the shadow of the kidney pelvis was otherwise normal.

Course in the Hospital: Because of previous failures of control, blood glucose determinations were made before each meal, with simultaneous determinations of urinary glucose. The quantity excreted in each four hour period was determined. The patient was offered a diet containing 175 grams of carbohydrate, 90 grams of protein, and 120 grams of fat, aggregating 1840 calories.

The daily loss of glucose ranged between 30 and 50 grams. There were four insulin reactions. Various combinations and dosages and insulin were tried but without success.

The urine became sterile after penicillin therapy, and at rest the blood pressure fell in a gradual manner to 135 millimeters of mercury systolic and 80 millimeters of mercury diastolic.

The advisability of nephrectomy was then considered. It had been shown that the patient was unable to remain well, avoid repeated insulin reactions, or acidosis. Hospital regulation at several institutions had failed. The recent course indicated that the diabetic state was becoming more difficult to control. It was suggested that nephrectomy would simplify diabetic control by allowing the patient to depend on urinary glucose determinations. The chronicity and likelihood of exacerbations of the right renal disease, the extensive x-ray changes, and poor phenol red excretion were further cited as reasons for right nephrectomy. Those opposed to the procedure argued that recurrent urinary tract infections could be controlled by chemotherapy, and that the excretory function of the kidney seemed quite adequate as measured by urea and creatinine clearances.

The probability that nephrectomy would relieve the recent semi-invalid state prevailed, and the right kidney was removed by Dr. Fred M. Hansen, Jr.

Pathological Observations: The right kidney weighed 190 grams. The lower pole of the kidney was shrunken, hard, and transversed by large depressed dark-based scars. Similar scars were seen at the upper pole. The mid-portion of the kidney was finely granular and, save for occasional depressed scars, appeared normal.

The pelvis had a capacity of 30 cubic centimeters.

Microscopic examinations showed infiltration of pelvic tissue by lymphocytes and plasma cells. Sections from the lower pole showed large numbers of fibrosed glomeruli, atrophic and dilated tubules, and medullary fibrosis. The blood vessel of this region showed advanced arteriosclerotic changes. Sections from the remainder of the kidney showed only occasional fibrosed glomeruli and atrophic tubules. Many afferent arterioles were thickened by a hyaline deposit. Stains with Best's carmine showed large masses of glycogen in the terminal portions of the proximal convoluted tubules.

The diagnoses were: Pyelonephritis, chronic active; hydronephrosis; arteriosclerosis of kidney, generalized.

Post-operative Course: Following surgery, there was acetonuria for two days. As soon as the patient could eat, her diabetic state was regulated with ease. Insulin dosage at the time of dismissal, 11 days after surgery, was 40 units of protamine zinc insulin and 25 units of crystalline insulin each morning. In the six months following nephrectomy her urine has contained glucose rarely, and then only following dietary indiscretion. She has experienced insulin reactions of a mild nature on two occasions as the insulin requirement fell to 20 units of protamine zinc insulin and 20 units of crystalline insulin each morning. Postoperative studies showed glycosuria to occur at blood glucose levels of 180 mg. per cent. At a blood glucose level of 150 mg. per cent there was no glycosuria. The urine has remained sterile. Blood pressure systolic has varied between 130 and 155 millimeters of mercury, and diastolic between 85 and 90 millimeters of mercury. No inference is drawn from the possible effect of nephrectomy on this individual's hypertension, inasmuch as the blood pressure had declined while she was at rest.

DISCUSSION

Early in the history of the knowledge of renal diabetes it was maintained that nephritis was one of the criteria necessary for the diagnosis of the disorder.⁸ However, Marble,⁹ in summarizing nine cases of renal diabetes and reviewing the literature, found general agreement that the renal function was normal in those cases fulfilling the criteria he proposed for the diagnosis of the state. Hawkins et al.¹⁰ found glycosuria in all cases of degenerative and advanced hemorrhagic glomerulonephritis, though blood glucose determinations following the oral injection of glucose were normal in all instances. Pierre-Bourgeois and Giraud¹¹ reported renal glycosuria in a patient with toxic nephritis following gold therapy. Helper and Simonds¹² observed glycosuria in dogs with nephritis following poisoning by uranyl nitrate. Steinitz,¹³ however, cited a patient with chronic nephritis who had decreased renal excretion of glucose when the blood glucose level was significantly elevated, and found the same condition in an individual with amyloidosis of the kidneys. Zinner¹⁴ presented cases which suggest that those with renal disease may have hyperglycemia without glycosuria.

In describing the anatomical pathology of one case of diabetes of renal type, Monasterio¹⁵ observed an anomaly characterized by an enormous dilatation of the renal tubules with flattening of the tubular epithelium. Cooke et al.¹⁶ found profound localized changes in the proximal convoluted tubules of an individual presenting the syndrome of osteoporosis, low serum phosphorus, and renal glycosuria. These pathological observations consisted of vacuolization of the cytoplasm and pyknosis of the nuclei of the cells with debris filling the lumen of the tubules.

Since it is known that the reabsorption of glucose occurs in the proximal convoluted tubules,¹⁷ one might expect such lesions to produce renal diabetes. It seems probable that such severe changes are not always present in this disorder for Friedman, Selzer, et al.¹⁸ found that at abnormally high blood glucose levels, the tubules of individuals with renal diabetes were able to reabsorb glucose at a rate equal to or exceeding those of individuals with presumably normal kidneys.

In this case, one is unable to determine whether or not the renal diabetes antedated the condition of hydronephrosis and pyelonephritis. However, it does seem reasonable that the ipsilateral conditions are related. Strong¹⁹ has shown

experimentally that severe anatomical changes occur in the proximal convoluted tubules of hydronephrotic kidneys out of proportion to rather minor visible glomerular changes. One might infer a decreased reabsorption of glucose by such tubules, although the amount of glomerular filtrate might be a little altered. McCance and Widdowson²⁰ have suggested the converse: a reduction in the glomerular filtrate in the presence of a more normal tubular reabsorptive mechanism to explain hyperglycemia without glycosuria in patients known to have renal disease. In this case, one is unable to infer that the glycogen masses found in the proximal convoluted tubules (Armanin-Ehrlich cells) contribute to the defect of glucose reabsorption. Farber, Berger, and Earle²¹ showed that in a group of middle-aged diabetic women, the glucose TM was actually increased.

The consistently increased amount of urine excreted by this kidney noted in this case suggests further impairment of reabsorptive capacity of the tubules. The ratio of volume of urine excreted by the right kidney to that excreted by the left remains about the same irrespective of rate of urine flow or of the concentration of glucose in urine at the moment.

SUMMARY

Unilateral renal glycosuria was discovered in a woman who had suffered from poorly controlled diabetes mellitus and chronic pyelonephritis for 12 years. Following nephrectomy the diabetic state has been controlled with ease, the urine has remained sterile, and the patient has been subjectively improved.

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EDITORIAL

THE RELATION OF CHOLESTEROL TO THE DEVELOPMENT OF ATHEROSCLEROSIS

INTEREST in the relationship of cholesterol to the development of arteriosclerosis dates from the demonstration by Aschoff more than 40 years ago that large amounts of cholesterol and other lipids are present in the atheromatous lesions of the aorta and its larger branches. This interest was greatly intensified by Anitschkow's report (1911) of the experimental production of similar atheromatous lesions in rabbits by feeding cholesterol for long periods. Anitschkow's observations have been abundantly confirmed, and a huge literature has accumulated on this subject.^{1, 2, 3} Although arterial lesions can be produced experimentally by other means, no other procedure has caused lesions closely resembling human atheroma, nor until recently had they been produced satisfactorily in any other species of animal.

These observations naturally led to the suggestion that cholesterol may in some way play a direct and perhaps essential rôle in the development of human atherosclerosis, and a considerable volume of evidence, largely indirect, has accumulated to support this hypothesis. This stems in part from animal experiments, also from the association of hypercholesterolemia with atherosclerosis in man. There is no substantial evidence to associate cholesterol with other types of arterial disease, such as the medial sclerosis seen characteristically in the peripheral arteries or the arteriolar changes of essential hypertension. This discussion is restricted to the atheromatous lesions. It will be convenient first to consider the experimental evidence.

Knowledge of the physiological rôle of cholesterol and of its metabolism is still incomplete. It is a constant and presumably essential constituent of the body cells and tissue fluids. It can be synthesized in amounts sufficient to meet the normal needs of the body. The only known exogenous source of cholesterol is animal fat, and in this form it is readily absorbed by the gastrointestinal tract. The related sterols in food of vegetable origin are believed to be absorbed in insignificant amounts if at all, and they are probably not utilized in the synthesis of cholesterol. Some mechanism, not adequately understood, undoubtedly exists which controls the cholesterol 'level' and provides for the elimination of an excess. Much is excreted in the bile, and although some is reabsorbed, a substantial amount is eliminated in the feces, largely after conversion to coprosterol by the intestinal bacteria. It is probable that some is also broken down in the tissues. Balance experiments have been reported which seemed to prove this, but they have been

¹ Leary, T.: The genesis of atherosclerosis, *Arch. Path.* **32**: 507-555, 1941.

² Hueper, W. C.: Arteriosclerosis (a general review), *Arch. Path.* **39**: 51 et seq., 1945.

³ Katz, L. N., and Dauber, D. V.: The pathogenesis of arteriosclerosis, *J. Mount Sinai Hosp.* **12**: 382, 1945.

questioned since it has been shown that cholesterol can be decomposed by intestinal bacteria.

The effectiveness of this mechanism evidently varies in different species of animals. In the rabbit, for example, it suffices for normal needs but breaks down readily under an overload. In the dog and cat, on the other hand, it is normally virtually impossible to overtax the mechanism by excessive feeding. Man seems to occupy a somewhat intermediate position but normally closer to the dog than to the rabbit.

If cholesterol in oil is fed to rabbits in large doses, the blood (plasma) cholesterol, normally in the range of 50 to 100 mg. per 100 c.c. rises markedly and may reach figures 10 to 20 times the normal. There is also a marked rise in other lipids. Animals sacrificed after four to six weeks show microscopic lesions and after eight to 10 weeks, gross localized atheromatous lesions in the aorta and some of its larger branches, including the coronary arteries, which closely but not precisely resemble the human lesions. In rabbits such lesions can be produced readily and predictably, although occasional individuals are resistant.

There has been controversy as to the factors which directly lead to the production of the lesions. The weight of evidence favors the imbibition theory. The plasma, containing cholesterol in a highly dispersed colloidal suspension, readily permeates the intima. If the cholesterol level is high, the suspension may be coarser, or local conditions in the intimal tissue may lead to the precipitation of the cholesterol in coarser particles which excite a local foreign body reaction and are gradually phagocyted by macrophages ("foam cells"). This view receives some support from analyses which show that the relative proportion of the different lipids in the lesions is essentially identical with that in the plasma. It is also supported by Hueper's observation² that lesions quite analogous to atheromas can be produced in rabbits by the intravenous injection of polyvinyl alcohol. This is a biologically inert material which forms a coarse colloidal suspension in the plasma and which is trapped like cholesterol in the interstices of the intima and is stored there in phagocytes as well as in other tissues. The introduction of lipids in phagocytes from extraneous sources has also been described (Leary¹ in rabbits, Katz and Dauber³ in chickens).

The localized character of the lesions and their precise distribution is best explained as the result of local mechanical strain and perhaps local turbulence of the blood stream which traumatize the tissues of the intima and favor the precipitation of cholesterol. Local anatomical peculiarities, possibly developed as a reaction to such strain, may also play a part (Winternitz).⁴

Some investigators have questioned whether the disease produced in rabbits is really comparable to that in man. The objection is raised that the rabbit is herbivorous, does not normally encounter cholesterol in its diet, and

⁴ Winternitz, M. C., et al.: Studies in pathology of vascular disease, *Am. Heart J.* 14: 399-404, 1937.

the conditions of the experiment are unnatural and artificial. There are certain differences in the nature and distribution of the lesions. In the rabbit the arch of the aorta is predominantly involved instead of the abdominal aorta, as in man, and the cerebral and renal arteries are rarely affected. Although the lesions in rabbits resemble reasonably well the earlier stages of atheroma in man, they do not develop the extensive fibrosis, calcification and ulceration seen in advanced human lesions. Furthermore in the rabbit cholesterol is deposited extensively in other organs, especially the liver and adrenal cortex, whereas this does not occur in man except in certain specific diseases accompanied by a gross disturbance of fat metabolism.

Undoubtedly the rabbit differs from man quantitatively if not qualitatively in its cholesterol metabolism. This is probably a peculiarity of the species, however, rather than a necessary consequence of its dietary habits. In the equally herbivorous guineapig atheroma can be produced only with difficulty and usually only as microscopic lesions. On the other hand Katz and Dauber⁵ showed that by feeding cholesterol to the omnivorous chick, atheroma can be produced with the greatest ease and regularity. The blood cholesterol rises promptly to high levels, six to 12 times the normal, and macroscopic lesions may be detectable after two weeks. They observed a direct relationship between the amount of cholesterol fed and the number and extent of the lesions.⁶ Similar lesions develop spontaneously in older birds. It is stated that such lesions do not appear until after the sixth month but were found in 45 per cent of the birds at one year of age. The atheroma produced in chickens resembles the human lesions more closely in character and distribution than does that in the rabbit.

In dogs, feeding cholesterol does not ordinarily raise the blood cholesterol or cause atheroma. Steiner and Kendall,^{6,7} however, found that the simultaneous administration of thiouracil brought about a marked elevation of the plasma cholesterol and after seven months to a year wide spread gross atheromatous lesions appeared. Their extent and severity varied with the height of the plasma cholesterol and the duration of the experiment. The distribution resembled that in man in affecting especially the abdominal aorta, and it included the coronary, cerebral and renal arteries. In some old lesions, calcification and hemorrhage were observed. One may conclude that, regardless of the rôle cholesterol may play in causing human atherosclerosis, these experimental lesions resemble those in man as closely as may reasonably be expected. There is, however, more extensive deposition of cholesterol in other tissues.

In man there is a high incidence of atherosclerosis, even in young individuals, in several metabolic disorders accompanied by a high plasma chole-

⁵ Horlick, L., and Katz, L. N.: The relationship of atheromatosis development in the chicken to the amount of cholesterol in the diet, *Am. Heart J.* **38**: 336-349, 1949.

⁶ Steiner, A., and Kendall, F. E.: Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil, *Arch. Path.* **42**: 433-444, 1946.

⁷ Steiner, A., Kendall, F. E., and Bevans, M.: Production of arteriosclerosis in dogs by cholesterol and thiouracil feeding, *Am. Heart J.* **38**: 34-42, 1949.

terol. These include nephritis in the nephrotic stage, myxedema and hypothyroidism, and particularly diabetes mellitus. In diabetes there is a much closer correlation with the duration of the disease than with its severity. There is evidence,⁸ however, that the incidence of atherosclerosis has been reduced in cases under good control on the low fat, high carbohydrate diets now generally employed.

The association of hypercholesterolemia and atherosclerosis is particularly striking in xanthomatosis (familial hypercholesterolemia), an inherited disturbance of metabolism, characterized clinically by cutaneous and occasionally visceral lesions, and frequently arcus senilis and symptoms of coronary arterial disease. Boas and Adlersberg⁹ reported a study of 64 members of seven families, 18 of whom showed the complete syndrome. Others, however, showed isolated manifestations of the disease, and in 50 of the 64 the plasma cholesterol was elevated. Several members of these families had died at an early age of coronary occlusion.

Boas and Parets¹⁰ reported a study of 122 cases of coronary arterial disease starting under 50 years of age. They were able to make satisfactorily extensive studies of 50 families from this group. In 15 families (30 per cent) all or most of the siblings examined had a high plasma cholesterol and in nine other families this was high in about half the members. In the remaining 26 families, no notable tendency to high figures could be demonstrated. These observations emphasize the importance of the hereditary factor, even in "uncomplicated" cases of atherosclerosis.

Many studies have been made of the plasma cholesterol in atherosclerosis in man, but the results, particularly of the earlier reports, have been contradictory. This is due in part to diagnostic difficulties. Neither "arteriosclerosis" (palpable thickening) of the peripheral vessels nor hypertension is a reliable criterion. Hypertension is common in patients with atherosclerosis, and if present it accelerates the development of the lesions, but fundamentally they are independent disturbances. The only reasonably reliable clinical manifestations of atherosclerosis are those of coronary arterial disease—angina and coronary thrombosis. Recent studies have been limited largely to this group.

Even these cases do not uniformly show a high plasma cholesterol. In some of the studies there was no statistically significant increase in the average level, particularly if reliance was placed on single or a few random determinations of the plasma cholesterol. More recently, however, a number of careful studies have been reported in which there was a significant increase in the average level above that in controls or above the usually accepted up-

⁸ Rabinowitch, I. M.: Arteriosclerosis in diabetes; relationship between plasma cholesterol and arteriosclerosis; effects of high carbohydrate-low caloric diet, *Ann. Int. Med.* **8**: 1436-1474, 1935.

⁹ Boas, E. P., and Adlersberg, D.: Familial hypercholesterolemia (xanthomatosis) and atherosclerosis, *J. Mount Sinai Hosp.* **12**: 84-86, 1945.

¹⁰ Boas, E. P., and Parets, A. D.: Hereditary disturbance of cholesterol metabolism in the genesis of atherosclerosis, *Am. Heart J.* **35**: 611-622, 1948.

per normal figure of 250 mg. per 100 c.c. Among these may be mentioned Davis et al.,¹¹ Lerman and White,¹² Boas and Parets,¹⁰ and Morrison et al.¹³ Lerman and White found plasma cholesterol above 240 mg. in 16 of 21 patients with coronary disease under 40 years of age. In Boas and Parets' series of 122 cases under 50 years, the cholesterol ranged from 199 mg. to 845 mg. with a mean of 316 mg. In 71 cases the level was above 300 mg. Morrison et al. studied 200 consecutive patients with acute coronary thrombosis. Elevated cholesterol levels were found in 48 per cent of 75 cases over 60 years of age and in 68 per cent of 125 cases under 60. Coronary occlusion occurred at an earlier age in individuals with a high plasma cholesterol.

Steiner and Domanski¹⁴ made repeated observations of the plasma cholesterol over periods up to two years in 15 cases of coronary disease and in 15 "relatively normal" controls. The average of the mean levels of the patients was 355 mg., 100 mg. higher than that of the controls. More significant was the difference in the variability of the levels in the two groups. In the normal group there was considerable difference in the blood levels of different subjects, but fluctuations in the same individual were relatively slight, whether made on different days or at different hours of the same day. In the patients with coronary disease, on the other hand, there were wide fluctuations in the plasma cholesterol, in some cases a series of upshoots from the normal range to pathological levels. The average difference between the maximum and minimum recorded for each individual was 100 mg., three times that in the control series.

These observations have recently been confirmed by Morrison, Hall and Gonzales.¹⁵ In a group of 30 normal controls followed for periods up to a year, fluctuations in the plasma cholesterol in individual cases were less than 10 per cent. In 50 patients with recent coronary thrombosis wide fluctuations were observed. Similar fluctuations reaching high levels occurred in a group of 30 miscellaneous patients, and Steiner and Turner¹⁶ have reported similar observations in 19 cases of pneumonia during late convalescence.

Such observations suggest that recurring episodes of hypercholesterolemia may be as significant as a sustained high blood level. If rabbits are fed large doses of cholesterol over recurrent periods of a few weeks separated by intervals of normal diet, successive crops of lesions may be produced or there may be evidence of acute exacerbations of the process in

¹¹ Davis, D., et al.: Lipid and cholesterol content of the blood of patients with angina pectoris and arteriosclerosis, *Ann. Int. Med.* **11**: 354-369, 1937.

¹² Lerman, J., and White, P. D.: Metabolic changes in young people with coronary heart disease, (Abst.) *Am. Soc. Clin. Invest.*, May 27, 1946.

¹³ Morrison, L. M., et al.: Cholesterol metabolism: Blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis, *Am. J. M. Sc.* **216**: 32-38, 1948.

¹⁴ Steiner, A., and Domanski, B.: Serum cholesterol level in coronary arteriosclerosis, *Arch. Int. Med.* **71**: 397-402, 1943.

¹⁵ Morrison, L. M., Hall, L., and Gonzales, W. F.: Significance of blood serum cholesterol instability in coronary arteriosclerosis, (Abst.) *Am. Heart J.* **38**: 478, 1949.

¹⁶ Steiner, A., and Turner, K. B.: Observations on the serum cholesterol in acute infections as recorded during and after pneumonia, *J. Clin. Invest.* **19**: 373-377, 1940.

old lesions. Similar pathologic evidence of recurrent attacks has been described in old human lesions. It seems likely that in man the disease advances by stages as the result of a series of insults rather than as a gradually progressive deterioration.

If the cholesterol in the plasma is a major factor in causing atherosclerosis, the effect of the ingestion of fat on the cholesterol level becomes a question of great practical importance. Many studies have been reported, again with contradictory results. The earlier work has been summarized by Rosenthal,¹⁷ who concluded that a high fat diet was almost invariably accompanied by a high rate of atherosclerosis. More recent studies suggest that neither a high fat nor a low fat diet over moderate periods has any notable effect on the cholesterol level in normal individuals. Neither did the addition of moderate amounts of cholesterol for short periods.¹⁸ By feeding 100 gm. of egg yolk powder to normal subjects on a high caloric diet for six to 10 weeks, however, Steiner and Domanski¹⁹ obtained elevations of 50 to 200 mg. in plasma cholesterol during the experimental period. Similar observations have been reported in dogs and rats but without the production of atheroma. Blotner (1935) and more recently Feinblatt²⁰ reported a rise in blood cholesterol and other lipids after a heavy fat meal in obese subjects but not in controls. In the "thin" group the alimentary hyperlipemia was confined largely to other lipids.

Moreton,²¹ among others, has emphasized the importance of the degree of dispersion of the colloidal lipid suspension. In diseases such as diabetes with high plasma cholesterol, this was uniformly found in coarse suspensions (milky plasma) containing lipid particles—"chylomicrons"—which are visible and can be counted with a dark-field microscope. In normal fasting plasma none was visible, but they were numerous for three to five hours after a fatty meal.

Attempts to work out a "cholesterol (or fat) tolerance test" thus far have not led to interpretable results. There is some evidence, however, that tolerance is reduced in patients with atherosclerosis. Morrison et al.²² found that after a fatty meal there was an abnormal rise in the serum lipid and a high chylomicron count in 25 cases of recent coronary thrombosis as compared with the controls. It seems quite possible that instability of the suspension may be more important than the actual concentration of cholesterol in producing atheromatous lesions.

¹⁷ Rosenthal, S. R.: Studies in atherosclerosis: chemical, experimental and morphologic; etc., *Arch. Path.* **18**: 473, 660, 827, 1934.

¹⁸ Turner, K. B., and Steiner, A.: A long term study of the variation of the serum cholesterol in man, *J. Clin. Invest.* **18**: 45-50, 1939.

¹⁹ Steiner, A., and Domanski, B.: Dietary hypercholesterolemia, *Am. J. M. Sc.* **201**: 820-824, 1941.

²⁰ Feinblatt, H. M.: Fat metabolism, *Am. J. Digest. Dis.* **11**: 260-261, 1944.

²¹ Moreton, J. R.: Physical state of lipids and foreign substances producing atherosclerosis, *Science* **107**: 371-373, 1948.

²² Morrison, L. M., et al.: Fat tolerance tests in coronary thrombosis, (Abst.) *Am. Heart J.* **38**: 477, 1949.

A low fat diet has little effect, if any, on the cholesterol level of normal individuals. In cases of xanthomatosis with very high serum cholesterol (500 to 1000 mg. or more) Thannhauser²³ found that a low fat diet continued for many weeks reduced the level markedly, but only while the diet was maintained. Kempner²⁴ reported that his rice diet caused a reduction in the plasma cholesterol in patients with hypertension, many of whom presumably had atherosclerosis. In 79 patients who had been on the diet for (on the average) more than five months, there was an average reduction of 78 mg. No report has been found of a systematic study of the long term effects of a low fat diet on the plasma cholesterol in cases of coronary arterial disease.

In chickens the administration of a fat-free mash retarded and reduced but did not prevent the spontaneous development of atherosclerosis as compared with controls on ordinary mash. It did not lower the plasma cholesterol.²⁵

Many attempts have been made to influence the cholesterol metabolism by means of drugs. Thyroid preparations administered in large doses to rabbits receiving cholesterol tend to prevent hypercholesterolemia and they retard and inhibit the development of atherosclerotic lesions. Thyroid has a similar effect in chickens, but it did not retard the appearance of spontaneous atheroma.²⁶ In man, thyroid has a potent effect in lowering plasma cholesterol. Its use for this purpose seems logical in cases with hypothyroidism, but few if any individuals could tolerate the doses required in the animal experiments.

These observations raise grave doubt as to the advisability of administering propylthiouracil to patients with atherosclerosis or cardiac disease, as some have recommended, unless they show clear evidence of hyperthyroidism.

The administration of potassium iodide or of organic iodides (Page²⁷) has a decided effect in inhibiting the development of experimental atherosclerosis in the rabbit. Iodides did not as a rule prevent hypercholesterolemia. These observations, which have been amply confirmed, support the view that some as yet unidentified factors, in addition to cholesterol, are essential for the production of the lesions. There is no evidence that any of these measures affects the established lesions.

Lipotropic agents have also been tried quite extensively, of which choline now seems the most promising. Negative results have been reported in

²³ Thannhauser, S. J., and Magendantz, H.: Different clinical groups of xanthomatous diseases; clinical physiological study of 22 cases, *Ann. Int. Med.* 11: 1662-1746, 1938.

²⁴ Kempner, W.: Treatment of hypertensive vascular disease with rice diet, *Am. J. Med.* 4: 545-577, 1948.

²⁵ Horlick, L., Katz, L. N., and Stamler, J.: The effect of a low fat diet on the spontaneously occurring arteriosclerosis of the chicken, *Am. Heart J.* 37: 689-700, 1949.

²⁶ Stamler, J., et al.: Studies on spontaneous and cholesterol-induced atherosclerosis and lipid metabolism in the chick. The effect of some lipotropic and hormonal factors, (Abst.) *Am. Heart J.* 38: 466, 1949.

²⁷ Page, I. H.: Some aspects of the nature of the chemical changes occurring in atheromatosis, *Ann. Int. Med.* 14: 1741-1755, 1941.

chickens.²⁶ In rabbits Brown et al.²⁸ and more definitely Steiner²⁹ have observed retardation and reduction in the extent of the atherosclerotic lesions. The degree of protection varied directly with the dose of choline administered. Hypercholesterolemia was not prevented, and the mode of action of choline is not known.

Morrison and Gonzales³⁰ administered choline in doses of six to 32 grams daily to 115 cases of "proved coronary thrombosis and myocardial infarction" for periods of one to three years. They had 115 alternate cases as controls. The mortality rate in their treated group was "significantly reduced." Their observations certainly warrant further controlled clinical trials, but they constitute a slim basis for the current advertising to the profession of choline preparations for the indiscriminate treatment of such cases.

The use of detergent or wetting agents has also been suggested, but no conclusions can now be drawn as to their value.

Also of interest is the report of Adlersberg et al.³¹ that large doses of lecithin from soy beans over periods of two to three months greatly reduced the marked hypercholesterolemia of four cases of xanthomatosis and one of diabetes.

Atherosclerosis should not be regarded as an inevitable manifestation of senility but rather as a specific disease of the arteries which may and too often does attack young individuals. Its greater incidence in the elderly may be due merely to greater opportunity for exposure to the agents or factors which produce it. The observations which have been reviewed both in experimental and human atherosclerosis constitute strong evidence that cholesterol is an important and probably an essential factor in its production, but not the only factor. An inherited constitutional tendency or defect is important in many cases. The immediate relationship of excessive fat intake to the factors which produce atheroma is somewhat less securely established, but there is highly suggestive evidence that this is significant, at least in some groups which may be regarded as predisposed.

It seems probable that the presence of cholesterol in a poorly dispersed unstable suspension is equally if not more significant than a mere increase in concentration. There is good evidence that this is a frequent sequel of a fatty meal, and repeated exposures over a period of years might well lead to the production of atheromatous lesions if the other requisite factors are operative. Restriction of fat seems indicated in predisposed individuals; those who already show manifestations of the disease, those who have a high

²⁸ Brown, G. O., et al.: Studies of the effect of lipotropic agents in experimental cholesterol atherosclerosis in the rabbit, (Abst.) *Am. Heart J.* **35**: 862, 1948.

²⁹ Steiner, A.: Effect of choline in the prevention of experimental aortic atherosclerosis, *Arch. Path.* **45**: 327, 1948.

³⁰ Morrison, L. M., and Gonzales, W. F.: Results of treatment of coronary arteriosclerosis with choline, (Abst.) *Am. Heart J.* **38**: 471, 1949.

³¹ Adlersberg, D., and Sobotka, H. J.: Effect of prolonged lecithin feeding on hypercholesterolemia, *J. Mount Sinai Hosp.* **9**: 955-956, 1943.

plasma cholesterol, whether sustained or intermittent, those who give a familial history of early or frequent coronary disease, and perhaps in simple obesity. On the other hand, an attempt so radically to alter the dietary habits of a large section of the population would be unwarranted, even if it were feasible.

Medicinal treatment is still in the earliest experimental stage, and no conclusions are warranted. Encouragement is to be derived from the active interest and intensive study already under way rather than from actual accomplishments. Man can not hope ever to avoid growing old. The hope is warranted, however, that from this work will come practicable measures which will delay and restrict the development of atherosclerosis and its most serious manifestation, coronary thrombosis.

P. W. C.

REVIEWS

Studies of Chronic Pyelonephritis with Special Reference to the Kidney Function.

By FLEMING RAASCHOU, Pathological Institute, Kommunehospital, Copenhagen.
260 pages; 18 × 25 cm. (paper bound). Ejnar Munksgaard, Copenhagen. 1948.
Price, Dan. kr. 20, —.

This monograph makes its most significant contribution in applying methods of estimating glomerular filtration and renal blood flow as well as the maximum tubular secretion to patients with chronic pyelonephritis. The first sections are concerned with the statistical analysis of 202 cases of macroscopically diagnosed pyelonephritis found among 3607 autopsies, of which 173 (85.7 per cent) were verified microscopically. Presumably all the material available for histologic examination was in accord with the macroscopic findings. One-third of the 202 patients showing the disease at autopsy gave no evidence of any other complicating pathology. Although chronic pyelonephritis occurred at all ages, it was mainly an adult affliction with a pronounced rise in incidence beyond the age of 60 years. The author offers a classification of pyelonephritis according to patho-anatomical characteristics which is for the most part in agreement with previous anatomical and clinical studies. He found no sex difference in the overall incidence of either atrophic or non-atrophic chronic pyelonephritis, but other lesions of the urinary tract which might have been primary to the pyelonephritis occurred twice as frequently among males as among females; that is, there was a preponderance of females among the cases where no extra-renal cause for the disease could be found. Clinical criteria for the diagnosis of chronic pyelonephritis are reviewed. The difficulties attending the clinical diagnosis of this disease are illustrated by the fact that of the cases observed at autopsy only one-sixth were clinically diagnosed before death.

The second part of the monograph deals with renal function tests on 21 females and 10 males in whom a clinical diagnosis of chronic pyelonephritis was made. Nine of these cases died subsequently and in these the diagnosis was verified macroscopically at post mortem. Unfortunately in only four of the nine cases was the microscopic examination of the kidneys reported.

Kidney function was evaluated by determinations of the urea clearance, inulin clearance, diodrast clearance and diodrast Tm. In addition plasma concentrations of albumin, globulin and non-protein nitrogen were measured. Values obtained in the patients were compared with those obtained on ten normal males and ten normal females. The author realizes the limitations of this control group composed of subjects considerably younger than his patient material and comments on the reduction in renal function in elderly subjects without clinical evidence of renal disease reported by others. The chemical procedures used were not the most sensitive or precise methods available. For instance, arbitrary correction factors were used for glucose and bound iodine.

Unfortunately the experimental design varied among individual subjects; 13 examinations were made after a single intravenous injection of inulin and diodrast. Another group of 13 tests was carried out by the constant infusion technic. In still other patients, diodrast titration curves were estimated using increasing blood levels of diodrast. In all 31 patients, inulin clearance varied from normal values of 143 c.c./min./1.73 sq. m. to 0.25 c.c. in one patient in uremic coma. It was found that the general clinical condition of the patient was not seriously affected until the inulin clearance dropped below 30 c.c. per minute. The author attributes the fall in inulin clearance to organic changes in the kidney resulting in obliteration of and interference

with the glomerular circulation. Urea was excreted in proportions normal to that of inulin.

Diodrast Tm values in these patients ranged from 42 mg. I/min./1.73 sq. m. to 0. Obvious clinical illness was not found until diodrast Tm values fell below about 7 mg. I/min. Many of the patients showed highly variable diodrast Tm values. Calculations of the ratio of inulin clearance to diodrast Tm indicated that tubular secretion of diodrast was much more affected than glomerular filtration in the advanced states of the disease. On the basis of a number of titration experiments with diodrast, the author concludes that in chronic pyelonephritis the self depression limit lies within normal ranges thus permitting the interpretation of values at low plasma levels as effective renal plasma flow. The evidence presented is presumptive but a definitive answer to this question could be given only on the basis of experimental determination of extraction ratios for diodrast based on catheterization of the renal vein in such patients. The diodrast clearance values range from 487 c.c./min./1.73 sq. m. to 13.1 c.c. Since the ratio of diodrast clearance to diodrast Tm showed normal values in the various phases of the disease, it was concluded that renal ischemia was not an important factor in the disease process. The author attributes the low diodrast clearances to the fall in maximum tubular secretion resulting from local abolition of secretion by the tubule. It is difficult to see why this should be true if the extraction ratio for diodrast in these patients is normal as postulated. It would seem more reasonable to attribute the reduction in diodrast clearance to a diminution in blood flow because of vascular changes.

In contrast to the findings in patients with hypertension, the filtration fraction was not consistently increased in patients with chronic pyelonephritis even in those cases complicated by arterial hypertension. The author believes that in the diseased kidney the remaining secretory tubular tissue behaves as completely normal renal tissue. This concept of sudden complete loss of function is difficult to accept.

Although the author attempts to use as diagnostic criteria for chronic pyelonephritis, a fall in glomerular filtration rate, renal plasma flow and diodrast Tm, the harsh facts of his data indicate that in some of the cases diagnosed clinically (and even anatomically) the values obtained in these functions fell well within the normal range observed in older people.

N. W. SHOCK

The Pathology of Articular and Spinal Diseases. By DOUGLAS H. COLLINS. 331 pages; 14.5 x 23 cm. The Williams and Wilkins Co., Baltimore. 1950. Price, \$7.00.

The purpose of this book, as set forth by the author in his preface, is to present an up-to-date and adequately illustrated account of the morbid anatomy of the joints and spine. In this he has succeeded surprisingly well. Dr. Collins has avoided getting involved in bone diseases and tumors except where essential to the pathological sequence of joint disease. As a result the book is not cluttered with overlapping kindred fields.

The chapter on the spine is most interesting, in particular the discussion on the origin and pathological physiology of the disc.

The text is magnificently and abundantly illustrated with photographs of pathological specimens and microscopic sections. What a pity the latter are not in color.

In all, this text is ideal for the orthopedist, a handbook for the pathologist and an excellent reference source for the medical man interested in joint and articular diseases.

L. A. K.

Surgical Treatment for Abnormalities of the Heart and Great Vessels. 1st Ed. By ROBERT E. GROSS, M.D., William E. Ladd Professor of Child Surgery, Harvard University Medical School. 72 pages; 14.5 x 22 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1950. Price, \$2.00.

This is an excellent monograph on the surgery of cardiovascular defects. Physiology, as well as anatomy of each subject is discussed in a concise and lucid manner.

Surgical technics are described and practical suggestions offered. The presentation of the experimental background of the modern surgical treatment of coarctation of the aorta should be invaluable to the clinician.

This book is well indexed and the bibliography is comprehensive. The liberal number of illustrations are clear cut and easily understood. Its compactness and small size, with large, clear print, make it a most desirable reference.

G. H. Y.

Treatment in Psychiatry. 2nd Ed. By OSKAR DIETHELM, M.D., Professor of Psychiatry, Cornell University Medical College. 546 pages; 15.5 x 23.5 cm. Charles C. Thomas, Publisher, Springfield, Illinois. 1950. Price, \$8.50.

This second edition of Dr. Diethelm's book has been completely rewritten since the first edition was published in 1936. The present edition is up-to-date and much more valuable because of this. The book is intended primarily for students who are specializing in psychiatry and for psychiatrists who teach in medical schools and clinics. Although the author follows pretty closely the school of thought developed by Adolf Meyer, he does give a fair description of other methods and schools of thought. This book is an excellent reference book and should be in every medical library but it is too detailed and specialized to be of much service to medical practitioners.

H. W. N.

The Origin of Medical Terms. By H. ALAN SKINNER, M.B., F.R.C.S. (Canada), Professor of Anatomy, University of Western Ontario. 379 pages. 17.5 x 26 cm. The Williams and Wilkins Company, Baltimore. 1949. Price, \$7.00.

This book is a mine of interesting information. Given the opportunity it will fill part of the cultural gap that is present in too many medical bookshelves and minds.

The book is a brief encyclopedia of usage in medicine and related subjects; it embraces etymology, biography and history. Some words, such as *glenoid*, have only etymological interest; others, such as *parotid*, require both derivation and a synopsis of the history of their use; while *Purkinje* clearly involves biography and history, but no etymology.

Little can be said except in praise. Dr. Skinner has undertaken a tremendous task "to place in the hands of medical students and those interested in medical terminology a general reference book of standard medical terms particularly those likely to be encountered by the medical student as he enters upon the study of medicine. While the material covers the general field of medicine it is particularly directed toward the basic medical sciences of anatomy, physiology, biochemistry and pathology." The author's purpose has been admirably achieved. The only valid criticisms are trivial—that a number of words, whose origins are either obscure or interesting, have been omitted: among these may be mentioned *viscosity*, *azotemia*, *ontology*; again, much more could be made of the interesting origin and history of such a word as allergy. Such omissions are emphasized by the disproportionate inclusion of unnecessary matter such as the quotation, under "ages," of 28 lines of Shakespeare (Jacques' famous speech). In several places there are misprints in the original Greek.

A student interested in medical origins may be faced with the problem of which book to get—this one, or Dr. Pepper's recent publication, *Medical Etymology*. Both are excellent works, and it may perhaps be profitable, without making invidious com-

parisons, to contrast the two. *Medical Etymology* is a smaller book and it is devoted, as its name implies, almost exclusively to word derivation; it is arranged by subjects (physiology, surgery, etc.) instead of in one alphabetical list, and is therefore slightly less easy to use; no Greek characters are employed; and there seem to be fewer omissions among words with interesting derivations. On the other hand, the present book contains many proper names with historical sketches which are not encompassed by *Medical Etymology*.

Dr. Skinner has included as an appendix a list of over 100 general sources from which his compilation was made. He has also added as further appendices the Greek Alphabet for the convenience of unfamiliar readers, and a table of the chemical elements with their discoverers.

The study of such a work as this makes for a more intelligent and interested understanding of medical terms and a more exact and careful use of scientific words. It cannot be too strongly recommended that this book should be widely studied; where it is studied it will inevitably be enjoyed.

H. J. L. M.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Abnormal Pneumoencephalogram. By LEO M. DAVIDOFF, M.D., Director of Neurological Surgery, Beth Israel Hospital, New York City, etc., and BERNARD S. EPSTEIN, M.D., Associate Radiologist, The Jewish Hospital of Brooklyn, Brooklyn, New York, etc. 506 pages; 25 × 17 cm. 1950. Lea & Febiger, Philadelphia. Price, \$15.00.

Actios of Amida: The Gynaecology and Obstetrics of the VIth Century, A.D., translated from the Latin Edition of Cornarius, 1542, and Fully Annotated. By JAMES V. RICCI, A.B., M.D., Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc. 215 pages; 24 × 15.5 cm. 1950. The Blakiston Company, Philadelphia. Price, \$7.00.

Annual Review of Medicine. Volume I. Editor: WINDSOR C. CUTTING, Stanford University School of Medicine; Associate Editor: HENRY W. NEWMAN, Stanford University School of Medicine. 484 pages; 23 × 15.5 cm. 1950. Annual Reviews, Inc., Stanford, California. Price, \$6.00.

Bacterial Infection, with Special Reference to Dental Practice. 4th ed. By J. L. T. APPLETON, B.S., D.D.S., Sc.D., Professor of Bacteriopathology and Dean, The Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania. 644 pages; 24 × 15.5 cm. 1950. Lea & Febiger, Philadelphia. Price, \$10.00.

Coronary Circulation in Health and Disease. By DONALD E. GREGG, M.S., Ph.D., M.D., Chief Research Physician, Medical Department, Field Research Laboratory, Fort Knox, Kentucky. 227 pages; 24 × 15.5 cm. 1950. Lea & Febiger, Philadelphia. Price, \$4.50.

Einführung in die Innere Medizin. 4th ed. By HANS JULIUS WOLF. 653 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$6.50.

Epidemics in Schools: An Analysis of the Data Collected During the Years 1935 to 1939. Medical Research Council Special Report Series No. 271. By E. A. CHEESEMAN. 96 pages; 24 × 15. cm. (paper-bound). 1950. His Majesty's Stationery Office, London. Price, 3 shillings net.

- Epidemiology in Country Practice.* By WILLIAM NORMAN PICKLES, M.D. (Lond.) Medical Officer of Health, Aysgarth Rural District; with a Preface by MAJOR GREENWOOD, F.R.S., D.Sc., F.R.C.P., Professor of Epidemiology and Vital Statistics in the University of London. 112 pages; 22 × 14 cm. Re-issued 1949 (first published May, 1939). The Williams and Wilkins Company, Baltimore. Price, \$2.50.
- The Ethical Basis of Medical Practice.* By WILLARD L. SPERRY, Dean of the Harvard Divinity School; with a Foreword by J. HOWARD MEANS, M.D. 185 pages; 21 × 14 cm. 1950. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$2.50.
- Funktionelle Diagnostik innerer Erkrankungen.* By DR. ANTON FISCHER and DR. CAMILLO SELLEI. 154 pages; 23 × 15.5 cm. (paper-bound). 1950. Springer-Verlag, Vienna. Price, \$2.80.
- Hilfstafern zur elektrokardiographischen Diagnostik.* By DR. ARNOLD HUTTMANN. 51 pages; 20 × 13 cm. (paper-bound). 1950. Verlag von Dr. Dietrich Steinkopff, Frankfurt/Main. Price, DM 8.—
- How to Stop Killing Yourself.* By PETER J. STEINCROHN, M.D. 272 pages; 19.5 × 13 cm. 1950. Wilfred Funk, Inc., New York. Price, \$2.95.
- Lipidoses: Diseases of the Cellular Lipid Metabolism.* By SIEGFRIED J. THANNHAUSER, M.D., Ph.D., Associate Professor of Medicine, Tufts College Medical School, etc.; edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (A.M.A.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. 605 pages (reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work); 24.5 × 16 cm. 1950. Oxford University Press, New York. Price, \$12.00.
- Non-Valvular Heart Disease.* By HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (A.M.A.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. 73 pages (reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work); 24 × 16 cm. 1950. Oxford University Press, New York. Price, \$2.00.
- Penicillin and Streptomycin in the Treatment of Infections.* By CHESTER S. KEEFER, M.S., M.D., Sc.D. (Hon.), Wade Professor of Medicine, Boston University School of Medicine, etc., and DONALD G. ANDERSON, M.D., Instructor in Medicine, Boston University School of Medicine, etc.; Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (A.M.A.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. 113 pages (reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work); 24 × 16 cm. 1950. Oxford University Press, New York. Price, \$2.50.
- The Rheumatic Diseases.* 3d ed. By G. D. KERSLEY, M.A., M.D. (Cantab.), F.R.C.P. (London), T.D., Director of Research and Advisor in Chronic Rheumatic Diseases to the South West and Oxford Regions, etc.; with a Foreword by SIR FRANCIS R. FRASER, M.A., M.D. (Ed.), F.R.C.P. (Lond.), Postgraduate Professor in Medicine to the University of London, etc. 143 pages; 22 × 14 cm. 1950. Grune & Stratton, New York. Price, \$3.50.
- Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung.* By PROF. DR. HANS SCHAEFER. 126 pages; 23 × 15.5 cm. (paper-bound). 1949. Verlag von Dr. Dietrich Steinkopff, Frankfurt/Main. Price, DM 48.—

COLLEGE NEWS NOTES

THIRTY-SECOND ANNUAL SESSION, A.C.P., ST. LOUIS, MO.

Plans are already well under way for the 32nd Annual Session, to be held in St. Louis, Mo., April 9-13, 1951. For those who wish to make advance hotel reservations, the officially designated hotels are listed below, together with their rates:

Hotel	For One Person	For Two Persons		2-Room Suites Parlor and Bedroom
		Double Bed	Twin Beds	
American	\$3.25-\$4.00	\$4.50-\$5.00	\$5.00-	\$8.00
Baltimore	3.00- 4.00	4.00- 5.00	5.00-\$6.00	
Chase	5.00- 8.00	7.00- 9.00	7.00-10.00	10.00-\$35.00
Claridge	3.25- 4.75	5.00- 7.50	5.50- 7.50	12.00 and up
DeSoto	3.50- 5.00	5.50- 8.00	7.00-13.00	12.00- 20.00
Forest Park	4.50- 5.00	6.50- 7.00	7.00 and up	10.00 and up
Jefferson	4.50- 6.50	6.00- 8.00	8.00- 8.50	12.00- 22.50
Kings-Way	4.00- 6.00	6.00- 7.00	6.50- 7.00	
Lennox	4.50- 6.75	5.25- 8.00	7.50- 8.00	11.00 and up
Majestic	3.00- 5.00	5.00- 6.00	7.00- 8.00	
Mark Twain	3.50- 5.50	5.50- 7.50	7.00- 8.00	
Mayfair	3.50- 8.50	5.00- 9.50	7.00 and up	14.00 and up
Melbourne	4.00- 6.00	6.50- 8.00	7.00- 9.00	12.00- 17.00
Park Plaza	6.00- 9.00	7.00-10.00	8.00-12.00	12.00- 20.00
Roosevelt	4.00- 5.00	5.00- 7.50	7.00- 8.00	12.00 and up
Sheraton	4.00- 6.00	6.00-10.00	7.35-11.00	9.00- 30.00
Statler	3.75- 6.50	5.25- 8.50	7.50-12.00	16.50- 19.50
Warwick	2.75- 3.25	3.80- 5.00	6.00	
York	3.00- 4.00	5.00- 5.50	5.50- 7.00	

All requests for reservations should be sent to:

Hotels Convention Reservation Bureau, A.C.P.
Room 406-911 Locust St.
St. Louis 1, Mo.

SPECIALTY BOARD EXAMINATIONS

The next scheduled oral examinations of the American Board of Pediatrics will be held in Chicago, Ill., October 13, 14 and 15, 1950, and in Boston, Mass., December 1, 2 and 3, 1950. Communications should be addressed to American Board of Pediatrics, Inc., 6 Cushman Rd., Rosemont, Pa.

The next examinations to be held by the American Board of Physical Medicine and Rehabilitation are scheduled for August 26 and 27, 1950, in Boston, Mass. Communications should be addressed to American Board of Physical Medicine and Rehabilitation, Attention: Dr. Robert L. Bennett, Secretary-Treasurer, 30 N. Michigan Ave., Chicago 2, Ill.

Examinations to be held by the American Board of Preventive Medicine and Public Health are scheduled for October 28 and 29, 1950, in St. Louis, Mo. Communications should be addressed to the American Board of Preventive Medicine and Public Health, Attention: Dr. Ernest L. Stebbins, Secretary, 615 N. Wolfe St., Baltimore 5, Md.

NEW LIFE MEMBER

The College is gratified to announce that Dr. Arthur E. Strauss, St. Louis, Mo., has become a Life Member of the American College of Physicians since the publication of the latest issue of this journal.

A.C.P. POSTGRADUATE COURSES

The postgraduate courses scheduled by the American College of Physicians for the fall, 1950, season are listed and described in the Advertising Section at the back of this issue.

A.C.P. REGIONAL MEETINGS

The list of scheduled Regional Meetings of the American College of Physicians, including dates and locations, is given in a full page announcement at the back of this issue.

LONG ISLAND COLLEGE OF MEDICINE CHANGES NAME

The Long Island College of Medicine was merged with the State University of New York on April 5, 1950, and henceforth will be known as the State University of the New York College of Medicine, State University Medical Center at New York. The College of Medicine is located at 350 Henry Street, Brooklyn.

CHICAGO MEDICAL SOCIETY OFFERS TWO POSTGRADUATE COURSES AUTUMN 1950

The Chicago Medical Society will offer two courses from October 23 through November 4, 1950, namely, "Diseases of the Gastrointestinal Tract, Liver, and Pancreas," during the week of October 23, and "Diseases of the Heart, Kidney and Blood Vessels," during the week of October 30. The courses will be given at Thorne Hall of Northwestern University Medical School. Tuition for each week is \$50.00, and the courses are open to all physicians who are members of their county medical societies. Outlines of the courses may be obtained from:

Committee on Postgraduate Medical Education
Chicago Medical Society
30 N. Michigan Ave.,
Chicago 2, Ill.

UNIVERSITY OF PENNSYLVANIA POSTGRADUATE COURSE

The University of Pennsylvania Graduate School of Medicine announces a new course, "Current Advances in Medicine and Surgery." This course will be an excellent, broad review of medicine and surgery during the past year, and it is planned that the course will be given annually. The first session will be from Monday, September 25, through Friday, September 29, 1950. The tuition fee will be \$100.00 for physicians in general; alumni of the Graduate School of Medicine are exempt and pay only a registration fee of \$10.00. All fees are payable on application. Full information and application form may be obtained through the Office of the Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pa.

REGULAR CORPS EXAMINATION, U. S. PUBLIC HEALTH SERVICE

A competitive examination for appointment of Medical Officers in the Regular Corps of the U. S. Public Health Service will be held on October 9, 10 and 11, 1950. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to the homes of the candidates. Applications must be received no later than September 11, 1950. Appointments will be made in the grades of Assistant Surgeon and Senior Assistant Surgeon. Application forms may be obtained by writing to the Surgeon General, U. S. Public Health Service, Federal Security Agency, Washington 25, D. C., Attention: Division of Commissioned Officers.

ARMY MEDICAL LIBRARY COLLECTS PHOTOGRAPHS OF A.C.P. FELLOWS

The Army Medical Library has a collection of more than 10,000 photographs and prints of medical men of the past four hundred years. It is its constant effort to enlarge this collection by securing portraits of contemporaries who have made significant contributions to the medical sciences. The Library through its Director, Major Frank B. Rogers (MC), solicits the portraits of all Fellows and Masters of the American College of Physicians. The address of the Library is 7th Street and Independence Avenue, S.W., Washington 25, D. C.

THE HUMAN HEART

The Heart Information Center, National Heart Institute, Bethesda 14, Md., has published a small booklet entitled, "The Human Heart," presenting information about the heart and diseases affecting the heart and circulatory system, understandable to the general public. The National Heart Institute states that it is issuing this pamphlet to meet the large number of requests from the public for such information. Single copies may be secured without charge.

Among the speakers at the annual meeting of the North Dakota State Medical Association, held in Grand Forks, N. D., May 27-30, were Dr. Nelson W. Barker, F.A.C.P., Rochester, Minn.; Dr. Robert B. Radl, F.A.C.P., Bismarck, Governor for North Dakota; Dr. Lester R. Dragstedt, F.A.C.P., Chicago, Ill.; Dr. Lester J. Palmer, F.A.C.P., Seattle, Wash. and Dr. Donald R. Nichols (Associate), Rochester, Minn.

Dr. John T. Farrell, F.A.C.P., Philadelphia, Pa., and Dr. James H. Means, F.A.C.P., Boston, Mass., were among the guest speakers at the annual meeting of the Rhode Island Medical Society held in Providence, May 10-11.

Dr. Robert S. Baldwin, F.A.C.P., Marshfield, Wis., was recently appointed Editor of the *Wisconsin Medical Journal*.

Dr. Kenneth E. Appel, F.A.C.P., Philadelphia, Pa., and Dr. Edgar Hull, F.A.C.P., New Orleans, A.C.P., Governor for Louisiana, were among the speakers at the annual meeting of the Oklahoma State Medical Association, held in Oklahoma City, June 4-7.

Dr. George E. Fahr, F.A.C.P., Professor of Medicine, University of Minnesota Medical School, was the speaker of the evening at the annual meeting of the Wisconsin Heart Association, held in Madison on June 10.

The School of Medicine and the Hospital of the University of Pennsylvania have established a psychiatric clinic for the treatment of juvenile patients with emotional disturbances. Dr. Kenneth E. Appel, F.A.C.P., Director of the Clinic, said that it would also serve as a training center for instruction of interns and resident physicians.

At the annual meeting of the Medical Association of the State of Alabama, Dr. James O. Finney, F.A.C.P., Gadsden, was elected Division Vice President.

Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, Governor for Northern California, was elected to the House of Delegates of the American Medical Association at the annual meeting of the California Medical Association.

Dr. Richard H. Young, F.A.C.P., Dean of the Northwestern University Medical School, presided over the ceremonies held in connection with the ground breaking for the Veterans Administration Research Hospital in Chicago on May 13. The hospital will become part of the Northwestern University Medical Center, and will cost \$14,000,000.

Dr. Robert M. Kark, F.A.C.P., Chicago, Ill., was promoted from Clinical Associate Professor to Professor of Medicine at the University of Illinois College of Medicine on July 1.

The fourth Community Nutrition Institute, sponsored by Syracuse University and the New York State Department of Health, was held at Syracuse University, June 10 to July 1. Among the speakers on the program were Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Mich., and Dr. G. Arnold Cronk (Associate), Syracuse.

The Hahnemann Medical College and Hospital of Philadelphia announced the appointment of Dr. Charles M. Thompson, F.A.C.P., as Professor and Head of the Department of Gastro-enterology. Dr. Thompson succeeds Dr. Harry M. Eberhard (Associate), who has retired.

Dr. James A. Halsted, F.A.C.P., Boston, Mass., has been appointed Section Chief at the Veterans Administration Hospital, Los Angeles, Calif. Dr. Halsted resigned his former position as Chief of Medical Service, Faulkner Hospital, Boston, Mass.

Cambridge University, England, conferred an honorary degree of Doctor of Science on Dr. William S. Middleton, F.A.C.P., President of the American College of Physicians, on June 8, 1950. The presentation oration said that Dr. Middleton, who was Consulting Physician to American forces in Europe during the war, worked with the British forces "in perfect amity and concord."

Captain Leon D. Carson (MC), USN, F.A.C.P., has been appointed Medical Officer in Charge of the U. S. Naval School of Aviation Medicine, Pensacola, Fla.

Dr. LeMoyné Copeland Kelly, F.A.C.P., New Haven, Conn., was elected as the first President of the newly-organized Connecticut Arthritis and Rheumatism Association, at a dinner meeting held in New Haven on May 22, 1950. At the same time Dr. W. Bradford Walker, F.A.C.P., Torrington, was elected Chairman of the Board of Trustees.

Dr. Joseph F. Worthen (Associate), Staten Island, N. Y., was awarded an honorary degree of Doctor of Humane Letters on June 3, 1950, at commencement exercises held at Wagner College. Dr. Worthen is an Attending Physician at the Staten Island Hospital and is a member of the Board of Trustees. He is President-elect of the Richmond County Medical Society.

Dr. Richard Dufficy Friedlander, F.A.C.P., Associate Clinical Professor of Medicine, University of California, School of Medicine, has been appointed Chief of the Unit of Internal Medicine and Chief Medical Consultant for the Regional Office of the Veterans Administration, San Francisco, Calif. One of Dr. Friedlander's duties will be the coordination and supervision of the newly formed special clinics in the various fields of internal medicine with the different consultants in these specialties.

He will continue his teaching and consultant activities at the University of California School of Medicine.

Dr. Spafford Ackerly, F.A.C.P., Professor of Psychiatry and Head of the Department at the University of Louisville School of Medicine, was given a surprise testimonial luncheon during the recent meeting of the American Psychiatric Association at Detroit. About 35 of Dr. Ackerly's colleagues, past presidents and fellows had planned this occasion for two years in honor of Dr. Ackerly's eighteen years of service in the University of Louisville and the City of Louisville. He was presented with a souvenir booklet bound in hand-tooled leather and containing a personal letter from each resident and fellow who had been trained under him. The spirit of the occasion was one of genuine affection and appreciation by those who had worked with and trained under Dr. Ackerly.

At the annual meeting of the American Psychiatric Association, held in Detroit, Mich., May 2-3, Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va., was elected Secretary.

The annual meeting of the American Diabetes Association was held in San Francisco, Calif., June 24-25, under the Presidency of Dr. Howard F. Root, F.A.C.P., Boston, Mass. Among the speakers were Dr. Jerome W. Conn, F.A.C.P., Ann Arbor, Mich., Dr. George W. Thorn, F.A.C.P., Boston, Mass., and Dr. Randall G. Sprague, F.A.C.P., Rochester, Minn.

At the recent annual meeting of the Connecticut State Medical Society, held in Waterbury, Dr. C. Charles Burlingame, F.A.C.P., Hartford, was named President-Elect, and Dr. Cole B. Gibson, F.A.C.P., Meriden, was re-elected Treasurer.

Dr. Warfield T. Longcope, F.A.C.P., Emeritus Professor of Medicine, Johns Hopkins University School of Medicine, presented the first Augustus B. Wadsworth Lecture on "Clinical Implications of Recent Advances in the Medical Sciences," in Albany, N. Y., May 24. The lectureship was established by the staff of the Division of Laboratories and Research of the New York State Department of Health and the Council of the New York State Association of Public Health Laboratories.

Dr. Robert H. Williams, F.A.C.P., Seattle, Wash., was guest speaker at the first annual meeting of the Spokane Society of Internal Medicine, held in Spokane, May 13.

OBITUARIES

DR. CHARLES FREDERICK TENNEY

Dr. Charles Frederick Tenney, F.A.C.P., who spent most of his medical life in New York City, died at Beverly Hills, California, on April 1, 1950. Dr. Tenney was born in Illinois on January 7, 1876; graduated from the University of Michigan Medical School in 1904. He devoted his work to the field of Internal Medicine from 1915 forward. At one time he was the Medical Director of the Toledo Hospital. He served during World War I as Chief of the Medical Service at the Base Hospital at Camp Upton, Long Island. He became Director of Medicine at the Fifth Avenue Hospital in New York City in 1922, serving until about 1936, when he became a Consultant in Medicine at that Institution.

It was in 1937 that he was elected the Governor of the American College of Physicians for Eastern New York, serving two successive terms, until 1942. At that time, he was made a Regent of the College and served on many important committees with distinction. His contributions to the College were numerous—immeasurable because many of them were directed toward the guidance, encouragement and inspiration of younger physicians preparing for a career in internal medicine.

Due to failing health, he retired from the Board of Regents at the New York Session in 1949, having moved at about this time to Beverly Hills, California, and entered upon full retirement from the practice of medicine.

ASA L. LINCOLN, M.D., F.A.C.P.

Governor for Eastern New York

DR. PATRICK LIAM LEDWIDGE

Patrick Liam Ledwidge, M.D., F.A.C.P., Detroit, Mich., was born May 18, 1890, and died April 15, 1950, following an attack of coronary occlusion the year before. He had been a Fellow of the American College of Physicians since 1926, and during World War II served as Acting Governor for Michigan. In addition to his work within the College, Dr. Ledwidge had many other medical and allied activities. He was for many years Assistant Physician, and more recently, Attending Physician to Harper Hospital. He was Consulting Physician to Mount Carmel Mercy Hospital, and Assistant Professor of Clinical Medicine in Wayne University College of Medicine. He was a Diplomate of the American Board of Internal Medicine since 1937.

Dr. Ledwidge was very active in the affairs of the Michigan State Medical Society. He was delegate to this society for nearly twenty years, and Speaker of the House of Delegates between 1943 and 1946. He became President of the Michigan State Medical Society in 1947, and served for one year. During this period of his activities he was very active in the affairs of Michigan Medical Service and most helpful in its development during those pioneer days.

In these trying days of medical economics, Dr. Ledwidge's advice and help will be sorely missed by those of us in Michigan.

DOUGLAS DONALD, M.D., F.A.C.P.,

Governor for Michigan

DR. ANDREW WALLHAUSER

Dr. Andrew Wallhauser, F.A.C.P., Wittman, Md., died at his home on April 5, 1950, age 57. Dr. Wallhauser was born at Newark, N. J., November 11, 1892. He received his medical training at Jefferson Medical College of Philadelphia, graduating in 1916. He was at one time an Assistant in Pathology at the Jefferson Medical College, but he early removed to Pittsburgh, Pa., and served for many years as Assistant Professor of Pathology and Bacteriology at the University of Pittsburgh

School of Medicine. He also held the rank of Assistant Professor of Medicine at the same institution and was Pathologist at the Presbyterian Hospital, the Woman's Hospital, and Associate Director of the Pennsylvania State Laboratory. Due to failing health, he retired from practice and from medical activity some three years ago and removed to Wittman, Md.

Although he resigned in later years from many of his medical societies, he had been a member of the Pittsburgh Academy of Medicine, the Pittsburgh Clinical Pathological Society for Biological Research and the American Association for the Advancement of Science. He served during the first World War with the famous Rainbow Division in France. He also served with the Essex Troup at the Mexican Border.

Dr. Wallhauser was a man of great personal charm, one who preferred to give than to receive, a scholar, a scientist, talented, alive, vibrant with the better things that in retrospect count so much. In the medical world he was best known for his work in Hodgkin's disease, his articles being published in the Archives of Pathology in 1933. They represented ten years of work and were considered a real contribution. He became a Fellow of the American College of Physicians in 1930.

EDWARD R. LOVELAND
Executive Secretary, ACP

DR. JAMES MONROE BAMBER

James Monroe Bamber, M.D., F.A.C.P., the dean of cardiologists in this area, died of coronary arteriosclerosis in New Orleans on March 14, 1950, at the age of 75. He is survived by his wife, the former Miss Verda Steen, and by three sisters and two brothers.

Dr. Bamber was born on August 5, 1874, in Tangipahoa Parish, La., the son of James Bamber and Rebecca Singleton. His boyhood there was not an easy one, but out of it came a man whom everyone respected for his integrity, simplicity and complete self-reliance. In addition to these personal qualities which made it impossible for him to wear any man's collar, he had the brain and the will to lift himself from rural obscurity to a position of urban power. After a primary education in his native community, he received the M.D. degree in 1908 from the Memphis Hospital Medical College, interned at the Memphis Hospital, and came to New Orleans nearly forty-five years ago. In 1916 he joined the Tulane University of Louisiana School of Medicine, became Professor of Clinical Medicine in 1938, retired from active teaching in 1940 because of poor health, and in 1948 was made Emeritus Professor of Medicine.

His published contributions are no measure whatever of the breadth and depth of his learning. While it may be said that he was largely self-taught, those who knew him best were convinced that he had no peer in American cardiology. He was an indefatigable reader, but he did his own thinking, relied upon his own experience, and in the end became one of the soundest and most dedicated consultants the South has ever seen.

THOMAS FINDLEY, M.D., F.A.C.P.,
Governor for Louisiana

DR. HERBERT NOBLE VERMILYE

Dr. Herbert Noble Vermilye, of Forest Hills, N. Y., died on April 12, 1950 of heart disease. He was born in Anniston, Ala. on Nov. 16, 1887. He graduated in 1910 from Princeton University, where he was Phi Beta Kappa; he received his M.D. degree from College of Physicians and Surgeons, N. Y. in 1914. Long a fellow of the American College of Physicians, he was also a member of the American

Medical Association, the Queens County Medical Society, fellow of the American College of Allergists, member of the Harvey Society, N. Y. Rheumatism Association, N. Y. Psychiatric Association, member and diplomate of the American Board of Internal Medicine. He served (1914-1915) as assistant to the house physician at St. Mary's Free Hospital for Children; was assistant and later (1920-1925) instructor in physiology at College of Physicians and Surgeons, N. Y. C. He served as assistant in medicine, assistant pediatrician, and from 1917-1936 as attending physician at Presbyterian Hospital. From 1936-1939 he was associate attending pediatrician at Fifth Avenue Hospital. During World War I he was associated (1917-1919) with the Presbyterian Hospital Medical Unit and attained the rank of major. During World War II he was on the Medical Advisory Board for selective service. Dr. Vermilye's interests in medicine were wide and at the time of his death he was actively pursuing investigations in chemotherapy and in the nature of allergic conditions.

DAVID P. BARR

DR. ARCHIBALD ALEXANDER BARRON

Archibald Alexander Barron, M.D., a Fellow of The College since 1923, was born November 4, 1886, in Rock Hill, S. C., and died in the Charlotte Memorial Hospital on February 8, 1950, after a coronary occlusion.

Dr. Barron attended Erskine College, Due West, S. C., and Vanderbilt University School of Medicine, receiving the M.D. degree in 1909. His postgraduate work included training at the University of Pennsylvania School of Medicine, New York Post-Graduate Medical School, and the University of Vienna Faculty of Medicine. He entered the practice of medicine in the field of neuropsychiatry, in Charlotte, N. C., in 1910, and was active until his death, except for a period of eighteen months during World War I when he served overseas as a Captain in Medical Unit O.

Dr. Barron was an active and influential member of the Charlotte Mental Hygiene Society and was largely instrumental in the establishment of the Charlotte Mental Hygiene Clinic. He was a pioneer in this field in the Charlotte area and contributed generously of his time, ability and finances to the advancement of the mental health of North and South Carolina.

Dr. Barron was a Fellow of the American Medical Association, ex-President of the North Carolina Neuropsychiatric Association, and member of the Southern Medical, the Southern Psychiatric and the American Psychiatric Associations. He was certified by the American Board of Internal Medicine and the American Board of Psychiatry and Neurology.

ELBERT L. PERSONS, M.D., F.A.C.P.,
Governor for North Carolina

DR. J. ARTHUR BUCHANAN

J. Arthur Buchanan, M.D., F.A.C.P., was born near Oxford, Pa., on September 7, 1887. He attended the public school in Elk Township, Chester County, Pa., and graduated in 1902. Then he attended Banks Business College, and was later graduated from Brown College Preparatory School in 1909. He started his medical studies at the University of Pennsylvania in 1909, and was graduated from the School of Biology in 1911, receiving his medical degree in 1915. At the time of his graduation he was awarded the Packard Prize in Internal Medicine and the Oliver Prize for studies in Diseases of the Eye. He was also elected to the Honorary Medical Fraternity, Alpha Omega Alpha.

Leaving Philadelphia, Dr. Buchanan went to Brooklyn, where he took his internship training at the Long Island College Hospital from 1915-1917. At the completion of his internship he was commissioned a Captain in the Medical Corps, U. S.

Army, and served until 1919. At the end of World War I he returned to his medical studies and was made a Fellow of the Mayo Clinic, where he remained until 1922. During this time he was elected to the Sigma Xi Fraternity. In 1922 he was awarded the degree of Master of Science in Medicine by the University of Minnesota. After completing his Fellowship at the Mayo Clinic, Dr. Buchanan went to Pueblo, Colo., where he was made Director of the Medical Department of the Pueblo Clinic. After two years in Pueblo he returned to Brooklyn, where he engaged in a very active practice in Flatbush for twenty-five years.

In Brooklyn Dr. Buchanan joined the Staff of the Wyckoff Heights Hospital, and was appointed Attending Physician in 1925. At the same time he was made Electrocardiologist, a position which he held until 1940. In 1941 he was made Director of Medicine of the Wyckoff Heights Hospital, and retained this position until the time of his retirement in 1948. He was Instructor at the Long Island College of Medicine from 1931-1936, and was Attending Physician at the Coney Island Hospital, where he was very active, from 1931-1945.

Dr. Buchanan was elected a Fellow of the American College of Physicians in 1939. Besides his great enthusiasm for medical knowledge, Dr. Buchanan enjoyed traveling. He traveled through European countries rather extensively and was very familiar with the habits and customs of the English, German, French and Italians. He was a great lover of opera, music and literature. He was the author of numerous articles in various medical journals.

Dr. Buchanan died April 17, 1950.

ASA L. LINCOLN,
Governor for Eastern New York

DR. ROY ROSS JAMIESON

Roy Ross Jamieson, Ph.C., M.D., F.A.C.P., of Chicago, Ill., died February 24, 1950. Dr. Jamieson was born in Goderich, Ont., Canada. He first graduated from the University of Minnesota in 1909 with the degree of Ph.C., then in 1913 was awarded the M.D. degree by the Northwestern University Medical School. He served on the faculty of his alma mater from 1918 until his death. During the year of 1929 he continued postgraduate studies at the University of Vienna.

In World War I Dr. Jamieson served as Lieutenant in the Medical Corps of the U. S. Army.

He served on many hospital staffs, from 1914 to 1927 with the Postgraduate Hospital and Medical School where he also taught postgraduate medicine; from 1918 to 1928 as Attending Physician at Wesley Memorial Hospital; in 1925 he became Chief of Staff at Washington Park Hospital; from 1933 to 1937 Attending Physician at the Cook County Hospital; during this period he was also Attending Physician to the Contagious Disease Hospital, and later was Chief of Staff at Jackson Park Hospital.

While teaching at Northwestern he became especially interested in diabetes and established the first diabetic clinic at that institution. He was one of the early diplomates of the American Board of Internal Medicine; a past president of his local branch of the Chicago Medical Society, and a member of the Illinois State Medical Society and the American Medical Association. He became a Fellow of the American College of Physicians in 1938.

In 1920 Dr. Jamieson married Sophia Andrews. Following in his footsteps and graduates of their father's alma mater, are Dr. Rodney Andrews Jamieson, who is specializing in internal medicine, and Dr. Robert Wallace Jamieson, who is specializing in surgery. All three survive their husband and father.

His colleagues recognized Dr. Jamieson as an able, devoted physician who was always willing to serve his brothers in his modest quiet manner. He was primarily a

bedside clinician, inspiring confidence in his patients and in his confreres. Conscientious to a fault, the welfare of his patient was his chief consideration. He will be remembered as a kindly physician who gave every ounce of his medical knowledge, and perhaps far too much of his physical strength, to the care of a large number of devoted patients.

JOSIAH J. MOORE, M.D., F.A.C.P.
LEROY H. SLOAN, M.D., F.A.C.P.

DR. ROBERT HAROLD JONES

Robert Harold Jones, M.D., F.A.C.P., died March 2, 1950, in a hospital in Pittsburgh, Pa., after a brief illness. Dr. Jones was born August 5, 1903, in Fairmont, W. Va. After attending West Virginia University, he taught school for several years before entering the Medical College of Virginia where he graduated with the degree of M.D. in 1933. He interned at the Baroness Erlanger Hospital in Chattanooga, Tenn., and did work in the T. C. Thompson Children's Hospital of that city. In 1935 he became associated with the medical staff at the Laird Memorial Hospital in Montgomery, W. Va., where he remained until 1941. He then returned to practice in his home town of Fairmont.

Dr. Jones served overseas in the 106th Station Hospital during World War II. He was separated from the service in 1946 with the rank of colonel.

He was a member of the Fairmont General and Fairmont Emergency Hospitals. He was a past president of the Fayette County Medical Society, a member of the American Medical Association, a former member of the Council of the West Virginia State Medical Association, and a member of the West Virginia Heart Association. He had been a Fellow in the American College of Physicians since 1942.

With the untimely death of Dr. Jones, West Virginia has lost one of her eminent physicians.

PAUL H. REVERCOMB, M.D., F.A.C.P.,
Governor for West Virginia

DR. OTTO MAIER

Otto Maier, Ph.G., M.D., died at Lenox Hill Hospital on March 9, 1950. Dr. Maier was born November 3, 1865, in Boettingen, Wuerttemberg, Germany. He was a graduate of New York College of Pharmacy in 1885, and of the Bellevue Hospital Medical College, 1891, with the degree of M.D. For a number of years, from 1898 to 1910, he was Instructor in Diseases of Children at New York Postgraduate Medical School and Hospital, and was also Consulting Pediatrician at St. Mark's Hospital, Visiting Physician at Lutheran Hospital, and later a member of the Courtesy Staff of the Lenox Hill Hospital. Dr. Maier had been a Fellow of the American College of Physicians since 1918. He was a member of the German Medical Society, the Yorkville Medical Society, and the Medical Jurisprudence Society, and a Fellow of the American Medical Association.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JAMES KINDRED NORMAN

James Kindred Norman, M.D., F.A.C.P., died at his home in Fort Worth, Tex., February 1, 1950, of carcinoma of the gallbladder.

Dr. Norman was born February 13, 1916, in Dardanelle, Ark. He received his academic education at Hendricks College, Conway, Ark., and was awarded a Bachelor of Science degree in 1940 by the University of Arkansas. In 1940 he was graduated from the University of Arkansas School of Medicine. He served an externship in

the University Hospital in Little Rock, and an internship at Charity Hospital in New Orleans, La., from 1940 to 1941. He did postgraduate work in New Orleans, New York, and Baltimore.

Entering the United States Public Health Service in 1941, Dr. Norman was stationed at Washington, D. C., Texarkana, Ark., New Orleans, La., Fort Worth, Tex., and Stapleton, N. Y. In 1946, after his discharge from the Public Health Service, he became associated with the Harris Clinic in Fort Worth, and maintained this connection until his death.

Dr. Norman was a member of the staff and teaching staff of the School of Nursing of the Harris Memorial Hospital. He was also a member of the staff of St. Joseph's and City-County Hospitals, of Fort Worth.

He was a member of the American Medical Association, Texas State Medical Association, Texas Heart Association, the American Heart Association and the Tarrant County Medical Society. He was a Diplomate of the American Board of Internal Medicine and was elected a Fellow of the American College of Physicians in 1947.

During his brief professional life, Dr. Norman had endeared himself to his colleagues, who held him in high esteem.

DAVID W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. VAUGHN LEE SHEETS

Vaughn Lee Sheets, M.D., F.A.C.P., was born in Willow, Va., October 2, 1869. He graduated from the Chicago College of Medicine and Surgery in 1903.

Dr. Sheets was Instructor in Physical Diagnosis at the Chicago College of Medicine and Surgery from 1903 to 1907. He was appointed Professor of Diagnosis and Clinical Medicine at the Chicago College of Medicine and Surgery in 1907 and held this position until 1921. Dr. Sheets was a Member of the Staff of Francis Willard Hospital from 1903 to 1939, and served as President of the Staff from 1917 to 1936. He became President of the Staff of the Walther Memorial Hospital in 1939.

Dr. Sheets was elected a Fellow of the American College of Physicians in 1920. He was a member of the Chicago Medical Society, the Illinois State Medical Society and a Fellow of the American Medical Association. His death on February 2, 1950, marked the termination of a long and active career in medicine in Chicago.

WALTER L. PALMER, M.D., F.A.C.P.,
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REGIONAL MEETING SCHEDULE

The American College of Physicians



<i>Territory</i>	<i>City</i>	<i>Date</i>	<i>Governor(s)</i>	<i>Comment</i>
NORTH DAKOTA	Minot	Sept. 9	Robert B. Radl, M.D.	Date to be announced.
WESTERN PENNSYLVANIA	Pittsburgh	Sept. 27	C. W. Morton, M.D.	To be held in conjunction with A.C.P. postgraduate course, "Internal Medicine."
OKLAHOMA-ARKANSAS	Tulsa	Sept. 30	Wann Langston, M.D. A. A. Blair, M.D.	
MISSISSIPPI	Jackson	Oct. 7	John G. Archer, M.D.	
ARIZONA	Tucson	Oct. 14	Leslie R. Kober, M.D.	Invitations extended to New Mexico and West Texas.
WESTERN NEW YORK	Rochester	Oct. 14	E. C. Reifenstein, M.D.	
PUERTO RICO	San Juan	Oct. 15	R. Rodriguez-Molina, M.D.	Date subject to change.
NORTHWEST	Portland, Ore.	Oct. 27-28	H. P. Lewis, M.D.	Includes Oregon, Washington, British Columbia, Alberta, with invitation to Manitoba, Saskatchewan, Idaho, Montana and Wyoming.
NEW JERSEY	Trenton	Nov. 1	Edw. C. Klein, Jr., M.D.	
UTAH	Salt Lake City	Nov. 11	Fuller B. Bailey, M.D.	Date subject to change. Meeting planned in conjunction with A.C.P. postgraduate course, "Recent Developments in Medicine."
MIDWEST	Madison, Wis.	Nov. 18	Karver L. Puestow, M.D., et al.	Includes Wisconsin, Illinois, Indiana, Iowa, Michigan, Minnesota, Ohio.
KENTUCKY	Lexington	Dec. 9	J. Murray Kinsman, M.D.	
SOUTHEAST	Charleston, S. C.	Jan. 26-27	Robert Wilson, Jr., M.D.	Includes South Carolina, Florida, Georgia, with invitation to Alabama.
NEBRASKA	Omaha	Feb. ?	J. D. McCarthy, M.D.	Exact date to be selected.
COLORADO	Denver	Feb. 20	Ward Darley, M.D.	Date subject to change.
KANSAS	Wichita	Mar. 16	W. C. Menninger, M.D.	
NORTHERN CALIFORNIA	San Francisco		Dwight Wilbur, M.D.	Date to be announced.
NORTH CAROLINA	Chapel Hill		Elbert Persons, M.D.	Date to be announced.
MIDSOUTH	New Orleans		Thomas Findley, M.D.	Date to be announced.
MONTANA-WYOMING	Billings, Mont.		H. W. Gregg, M.D.	Date to be announced.

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POSTGRADUATE COURSES

Autumn Schedule, 1950

THE AMERICAN COLLEGE OF PHYSICIANS

Course No. 1, INTERNAL MEDICINE: SELECTED SUBJECTS. University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; one week, September 25-30. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

Course No. 2, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. Duke University School of Medicine, Durham, N. C.; Eugene A. Stead, Jr., M.D., F.A.C.P., Director; one week, October 9-14. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

Course No. 3, CRITICAL PROBLEMS IN INTERNAL MEDICINE. University of Chicago School of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director; one week, October 23-27. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

Course No. 4, CLINICAL ALLERGY. Roosevelt Hospital Institute of Allergy, New York, N. Y.; Robert A. Cooke, M.D., F.A.C.P., Director; two weeks, October 23-November 3. Fees: A.C.P. Members, \$120.00; Non-members, \$240.00.

Course No. 5, RECENT DEVELOPMENTS IN MEDICINE. University of Utah College of Medicine, Salt Lake City, Utah; Max M. Wintrobe, M.D., F.A.C.P., Director; one week, November 6-11. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

Course No. 6, PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION. Mayo Clinic and Mayo Foundation, Rochester, Minn.; Walter F. Kvale, M.D., F.A.C.P., Director; and Edgar V. Allen, M.D., F.A.C.P., Nelson W. Barker, M.D., F.A.C.P., John E. Estes, M.D., Edgar A. Hines, Jr., M.D., F.A.C.P., and Richard M. Shick, M.D., F.A.C.P., Co-Directors; one week, November 27-December 2. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

Course No. 7, GASTRO-ENTEROLOGY. University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week, December 4-9. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

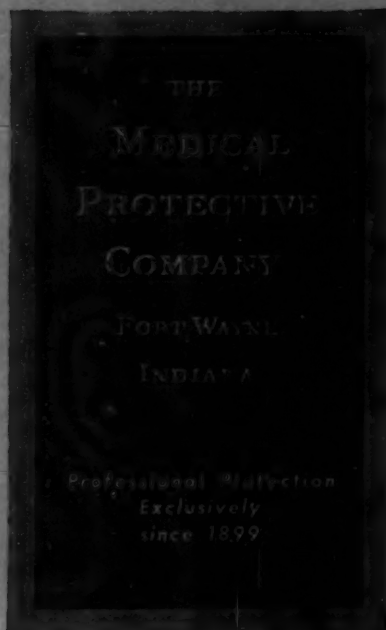
Course No. 8, HEMATOLOGY. New England Medical Center, Boston, Mass.; William Dameshek, M.D., F.A.C.P., Director; one week, December 11-16. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

Course No. 9, MODERN TRENDS IN THE DIAGNOSIS AND TREATMENT OF HEART DISEASE. Woman's Medical College of Pennsylvania and other Philadelphia institutions, Philadelphia, Pa.; William G. Leaman, Jr., M.D., F.A.C.P., Director; one week, January 22-27, 1951. Fees: A.C.P. Members, \$30.00; Non-members, \$60.00.

A course in Electrocardiography previously proposed at Wayne University College of Medicine, Detroit, Mich., under the directorship of Gordon B. Myers, M.D., F.A.C.P., must be delayed until 1951.

For detailed outlines of courses, hotel accommodations and other information, including registration forms, send inquiries to

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4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

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REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

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